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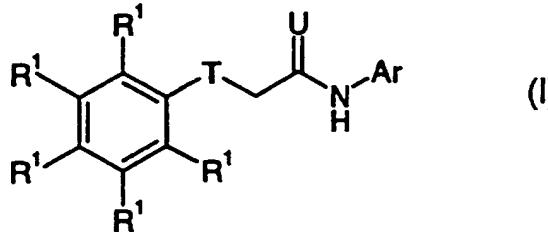
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(54) Title: SUBSTITUTED PHENYL COMPOUNDS WITH IMMUNOSUPPRESSING ACTIVITY AND PHARMACEUTICAL COMPOSITIONS



(57) Abstract: The invention provides substituted phenyl compounds of general formula (I) wherein R¹, T, U and Ar are as defined in the specification, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

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SUBSTITUTED PHENYL COMPOUNDS WITH IMMUNOSUPPRESSING ACTIVITY AND PHARMACEUTICAL COMPOSITIONS

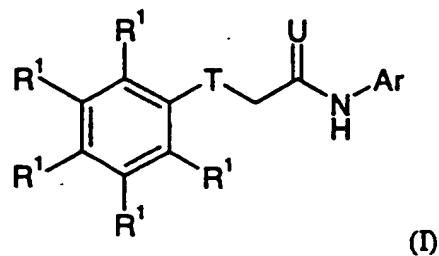
The present invention relates to substituted phenyl compounds, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

The P2X₇ receptor (previously known as P2Z receptor), which is a ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the P2X₇ receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1 β (IL-1 β) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and proliferation (T cells), apoptosis and L-selectin shedding (lymphocytes). P2X₇ receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells), hepatocytes and mesangial cells.

Certain substituted acetamide compounds are known from EP-A-382 216 having anti-allergic activity.

It would be desirable to make compounds effective as P2X₇ receptor antagonists for use in the treatment of inflammatory, immune or cardiovascular diseases, in the aetiologies of which the P2X₇ receptor may play a role.

In accordance with the present invention, there is therefore provided a compound of general formula



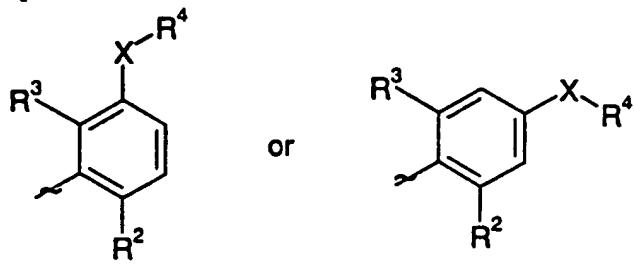
wherein:

each R¹ independently represents a hydrogen or halogen (e.g. fluorine, chlorine, bromine or iodine) atom, or a trifluoromethyl, cyano, nitro, C₁-C₆ alkyl or C₁-C₆ alkoxy group;

T represents an oxygen atom or, preferably, a group NH;

5 U represents an oxygen or sulphur atom or a group NH, preferably an oxygen or sulphur atom;

Ar represents a group



X represents a bond, an oxygen atom or a group CO, CH₂, CH₂O, O(CH₂)_m,

10 CH₂OCH₂, NR⁵, CH₂NR⁵, NR⁵CH₂, CH₂NR⁵CH₂, CONR⁵, S(O)_n or SO₂NR⁵;

m is 1, 2 or 3;

n is 0, 1 or 2;

one of R² and R³ represents a halogen, cyano, nitro, amino, hydroxyl, or a group selected from C₁-C₆ alkyl optionally substituted by at least one C₃-C₆ cycloalkyl,

15 C₃-C₈ cycloalkyl, C₁-C₆ alkyloxy optionally substituted by at least one C₃-C₆ cycloalkyl, C₃-C₈ cycloalkyloxy, S(O)_pC₁-C₆ alkyl or S(O)_qC₃-C₈ cycloalkyl, each of these groups being optionally substituted by one or more fluorine atoms, and the other of R² and R³ represents a hydrogen or halogen atom or a methyl group;

p is 0, 1 or 2;

20 q is 0, 1 or 2;

R⁴ represents di(C₁-C₂ alkyl)N(CH₂)_t where t is 0, 1 or 2 or imidazolyl, or R⁴ represents a 3- to 9-membered saturated heterocyclic ring system containing one or two nitrogen atoms, the heterocyclic ring system being optionally substituted by one or more substituents independently selected from fluorine atoms, hydroxyl, C₁-C₆ alkyl, acetyl, hydroxyC₁-C₆ alkyl, -NR⁶R⁷, -(CH₂)_rNR⁶R⁷, -CONR⁶R⁷ and pyrimidinyl,

or R^4 represents a 3- to 8-membered saturated carbocyclic ring system substituted by one or more substituents independently selected from NR^6R^7 , $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$, the ring system being optionally further substituted by one or more substituents independently selected from fluorine atoms, hydroxyl and C_1 - C_6 alkyl;

5 r is 1, 2, 3, 4, 5 or 6;

R^5 represents a hydrogen atom or a C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl group; and

10 R^6 and R^7 each independently represent a hydrogen atom or a C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl group, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring, provided that when R^3 represents a cyano group, then X is other than a bond;

15 or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise indicated, an alkyl substituent or alkyl moiety in a substituent group may be linear or branched. When one of 15 R^2 and R^3 represents a C_1 - C_6 alkyl/ C_1 - C_6 alkyloxy optionally substituted by at least one C_3 - C_6 cycloalkyl, it should be understood that one or both of the alkyl and cycloalkyl moieties may be optionally substituted by fluorine atoms. A 3- to 9-membered saturated heterocyclic ring system containing one or two nitrogen atoms may be a monocyclic or bicyclic ring system. Similarly, a 3- to 8-membered saturated carbocyclic ring system may 20 be a monocyclic or bicyclic ring system. The hydroxyl moiety in a hydroxyalkyl substituent group may be located in any suitable position in the alkyl group. Typically, the hydroxyl moiety will be located on a terminal carbon atom in a straight chain alkyl group. The alkyl groups in a dialkylamino moiety may be the same or different.

25 Preferably, at least one group R^1 is other than a hydrogen atom, especially a halogen atom such as a fluorine or chlorine atom.

Preferably X represents a bond, an oxygen atom or a group $CONH$, CH_2 or $O(CH_2)_m$.

One of R^2 and R^3 represents a halogen (e.g. fluorine, chlorine, bromine or iodine), cyano, nitro, amino, hydroxyl, or a group selected from C_1 - C_6 alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl) optionally substituted by at least one (e.g. 1, 2 or 3) C_3 - C_6 cycloalkyl (i.e. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl),

5 C_3 - C_8 cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), C_1 - C_6 alkyloxy (e.g. methoxy, ethoxy, isoproxy or tert-butoxy) optionally substituted by at least one (e.g. 1, 2 or 3) C_3 - C_6 cycloalkyl (i.e. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), C_3 - C_8 cycloalkyloxy (e.g. cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or cyclohexyloxy), $S(O)_pC_1$ - C_6 alkyl (e.g. $S(O)_p$ methyl, -ethyl, -propyl, -butyl, -pentyl or -hexyl) or $S(O)_qC_3$ - C_8 cycloalkyl (e.g. $S(O)_q$ cyclopropyl, -cyclobutyl, -cyclopentyl or -cyclohexyl), each of these groups being optionally substituted by one or more (e.g. 1, 2, 3 or 4) fluorine atoms, and the other of R^2 and R^3 represents a hydrogen or halogen (e.g. fluorine, chlorine, bromine or iodine) atom or a methyl group.

10

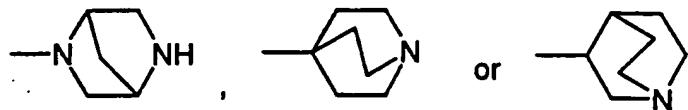
15 Preferably, one of R^2 and R^3 represents a halogen (especially chlorine) atom or a C_1 - C_6 alkyl (especially methyl) group and the other of R^2 and R^3 represents a hydrogen atom.

20 In one aspect, R^4 may represent a 3- to 9-membered saturated heterocyclic ring system containing one or two nitrogen atoms, the heterocyclic ring system being optionally substituted by one or more (e.g. 1, 2, 3 or 4) substituents independently selected from fluorine atoms, hydroxyl, C_1 - C_6 alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl), acetyl, hydroxy C_1 - C_6 alkyl (e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl or hydroxyhexyl), $-NR^6R^7$, $-(CH_2)_rNR^6R^7$, $-CONR^6R^7$ and

25 pyrimidinyl.

25 The 3- to 9-membered saturated heterocyclic ring system in the group R^4 may be a monocyclic ring system such as a pyrrolidinyl (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl or 3-pyrrolidinyl), piperidinyl (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl or

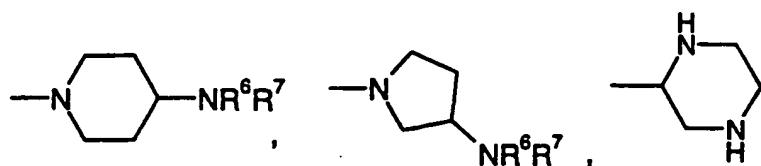
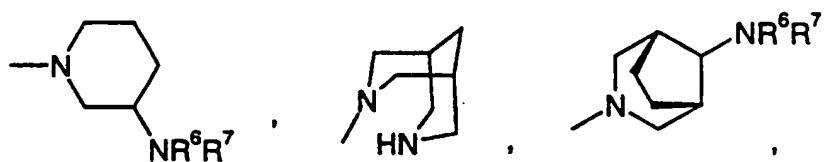
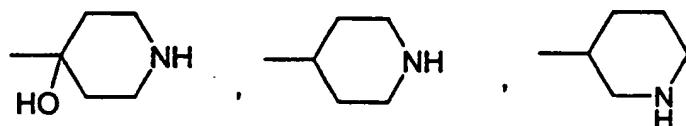
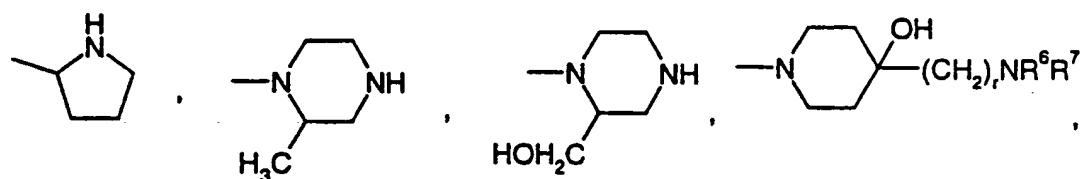
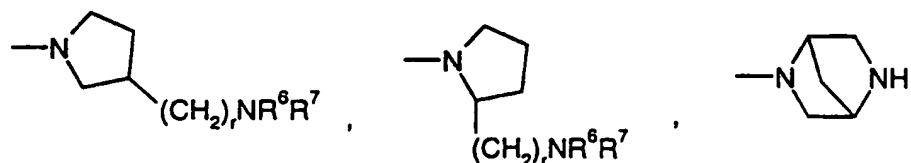
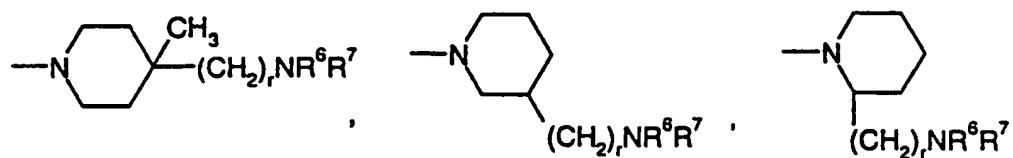
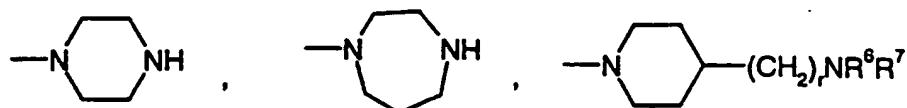
4-piperidinyl), piperazinyl (e.g. 1-piperazinyl) or homopiperazinyl ring, or a bicyclic ring system such as

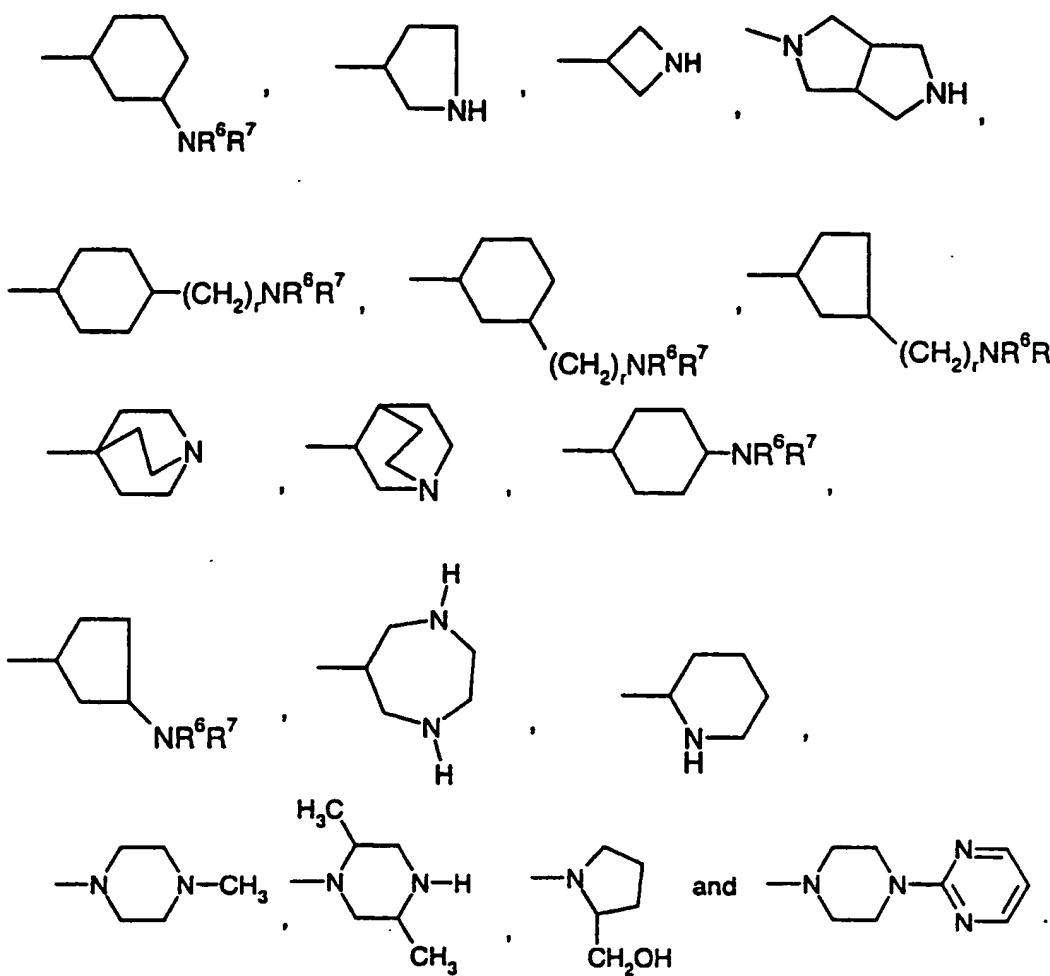


5 In another aspect, R^4 may represent a 3- to 8-membered saturated carbocyclic ring system substituted by one or more (e.g. 1, 2 or 3) substituents independently selected from NR^6R^7 , $-(CH_2)_fNR^6R^7$ and $-CONR^6R^7$, the ring system being optionally further substituted by one or more (e.g. 1, 2, 3 or 4) substituents independently selected from fluorine atoms, hydroxyl and C_1 - C_6 alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or
10 hexyl).

The 3- to 8-membered saturated carbocyclic ring in the group R^4 is preferably a monocyclic ring system such as a cyclopentyl or cyclohexyl ring.

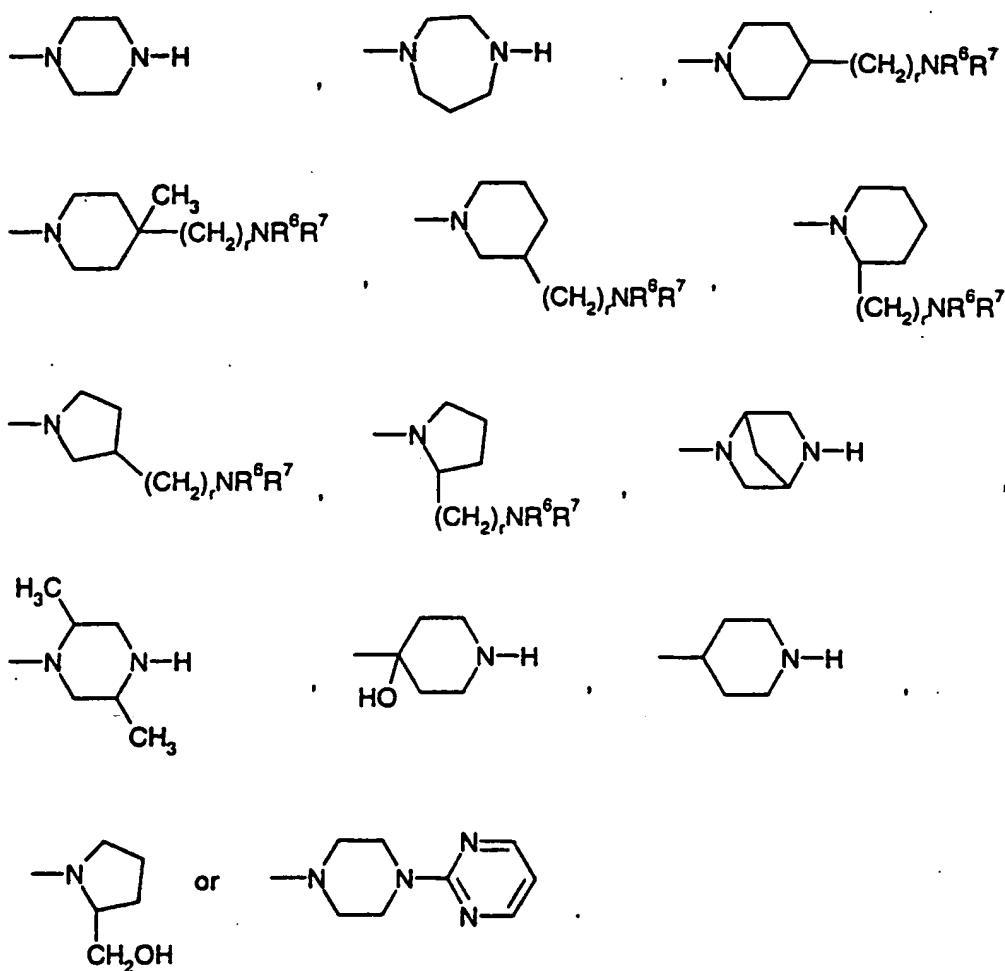
15 Specific examples of groups R^4 include:



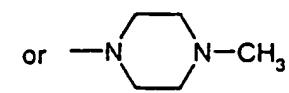
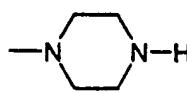
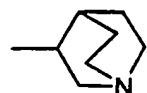
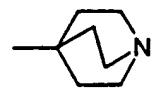
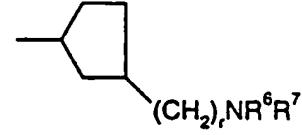
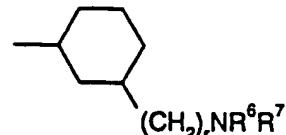
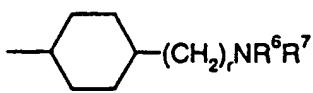
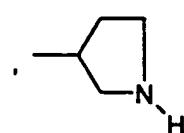
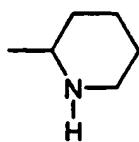
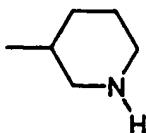
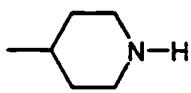


When X represents a bond or a group CO, CH₂ or SO₂, R⁴ preferably represents a

5 group:



When X represents an oxygen or sulphur atom or a group CH_2O , $\text{O}(\text{CH}_2)_m$, CH_2OCH_2 , NR^5 , CH_2NR^5 , NR^5CH_2 , $\text{CH}_2\text{NR}^5\text{CH}_2$, CONR^5 , SO or SO_2NR^5 , R^4
⁵ preferably represents a group:



R^5 represents a hydrogen atom, or a C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl) or C₃-C₈, preferably C₃-C₆, cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) group.

R^6 and R^7 each independently represent a hydrogen atom, or a C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl) or C₃-C₈, preferably C₃-C₆, cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) group, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring such as a pyrrolidinyl or piperidinyl ring.

Preferred compounds of the invention include:

2-(3,4-Difluorophenylamino)-N-(2-methyl-5-piperazin-1-ylmethyl-phenyl)-acetamide, trihydrochloride,

2-(3,4-Difluoro-phenylamino)-N-(2-methyl-5-piperazin-1-ylmethyl-phenyl)-thioacetamide,

2-(3,4-Difluoro-phenylamino)-N-(2-methyl-4-piperazin-1-ylmethyl-phenyl)-acetamide, trihydrochloride,

N-(2-Chloro-5-piperazin-1-yl-phenyl)-2-(3,4-difluoro-phenylamino)-acetamide, trihydrochloride,

(*S*)-2-(3,4-Difluoro-phenylamino)-*N*-(2-methyl-4-(2-pyrrolidin-1-ylmethyl-pyrrolidin-1-ylmethyl)-phenyl)-acetamide, trihydrochloride,

5 2-(3-Chloro-4-fluorophenylamino)-*N*-(2-methyl-5-[3-(4-methylpiperazin-1-yl)-propoxyl]phenyl)acetamide,

(+/-)-2-(3-Chloro-4-fluoro-phenylamino)-*N*-(2-methyl-5-(piperidin-4-yloxy)-phenyl)-acetamide, dihydrochloride,

10 2-(3,4-Difluoro-phenylamino)-*N*-(2-methyl-4-(piperidin-4-yloxy)-phenyl)-acetamide, dihydrochloride,

(\pm)*N*-[5-(3-Amino-pyrrolidin-1-yl)-2-methyl-phenyl]-2-(3,4-difluoro-phenylamino)-acetamide, trihydrochloride,

15 2-(3,4-Difluoro-phenylamino)-*N*-(2-methyl-5-piperazin-1-yl-phenyl)-acetamide, trihydrochloride,

(*S*)-2-(3,4-Difluoro-phenylamino)-*N*-(2-methyl-5-(2-pyrrolidin-1-ylmethyl-pyrrolidin-1-ylmethyl)-phenyl)-acetamide,

20 (S)-2-(3,4-Difluoro-phenylamino)-*N*-(5-(2-hydroxymethyl-pyrrolidin-1-ylmethyl)-2-methyl-phenyl)-acetamide,

2-(3,4-Difluoro-phenylamino)-*N*-(2-methyl-5-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-phenyl)-acetamide,

25 2-(3,4-Difluorophenylamino)-*N*-(2-methyl-3-(piperidin-4-yloxy)phenyl)acetamide trifluoroacetate,

30 3-[2-(3,4-Difluorophenylamino)acetyl-amino]-*N*-(2-dimethylaminoethyl)-2-methylbenzamide,

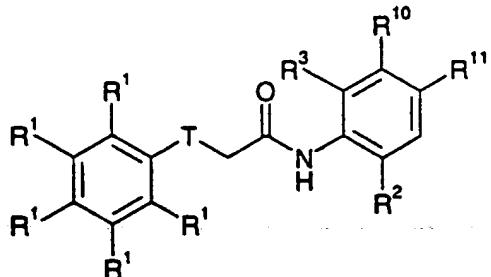
N-[3-(4-Acetyl-piperazin-1-ylmethyl)-2-methylphenyl]-2-(3,4-difluorophenylamino)acetamide,

2-(3,4-Difluorophenylamino)-*N*-(3-imidazol-1-ylmethyl-2-methylphenyl)acetamide, and

35 2-(3,4-Difluorophenylamino)-*N*-(3-dimethylaminomethyl-2-methylphenyl)acetamide.

The present invention further provides a process for the preparation of a compound of formula (I) as defined above which comprises:

(i) when U represents an oxygen atom, X represents a CH_2 group and R^4 represents a 3- to 8-membered saturated heterocyclic ring system containing one or two nitrogen atoms, the heterocyclic ring system being optionally substituted by one or more substituents independently selected from fluorine atoms, hydroxyl, $\text{C}_1\text{-C}_6$ alkyl, hydroxy $\text{C}_1\text{-C}_6$ alkyl, $-\text{NR}^6\text{R}^7$, $-(\text{CH}_2)_t\text{NR}^6\text{R}^7$, $-\text{CONR}^6\text{R}^7$ and pyrimidinyl, reacting a compound of general formula



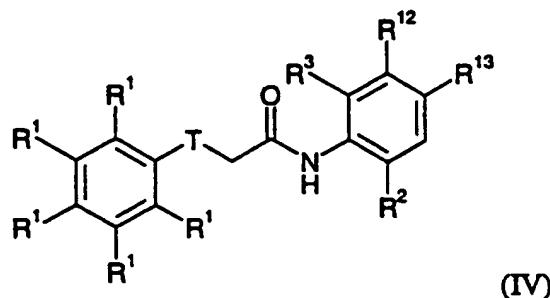
(II)

wherein one of R^{10} and R^{11} represents a hydrogen atom and the other of R^{10} and R^{11} represents a group $-\text{CH}_2\text{L}^1$ in which L^1 represents a leaving group (e.g. a halogen atom), and T , R^1 , R^2 and R^3 are as defined in formula (I), with a compound of general formula



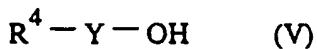
in the presence of a base (e.g. diisopropylethylamine), wherein $\text{R}^{4'}$ represents a 3- to 8-membered saturated heterocyclic ring system containing one or two nitrogen atoms, the heterocyclic ring system being optionally substituted by one or more substituents independently selected from fluorine atoms, hydroxyl, $\text{C}_1\text{-C}_6$ alkyl, hydroxy $\text{C}_1\text{-C}_6$ alkyl, $-\text{NR}^6\text{R}^7$, $-(\text{CH}_2)_t\text{NR}^6\text{R}^7$, $-\text{CONR}^6\text{R}^7$ and pyrimidinyl and wherein R^6 and R^7 are as defined in formula (I); or

(ii) when U represents an oxygen atom and X represents an oxygen atom or a group $\text{O}(\text{CH}_2)_m$, reacting a compound of general formula



wherein one of R^{12} and R^{13} represents a hydrogen atom and the other of R^{12} and R^{13} represents a hydroxyl group, and T , R^1 , R^2 and R^3 are as defined in formula (I), with a compound of general formula

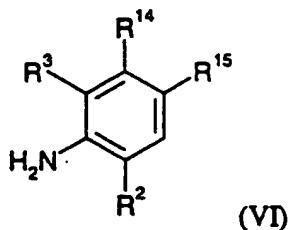
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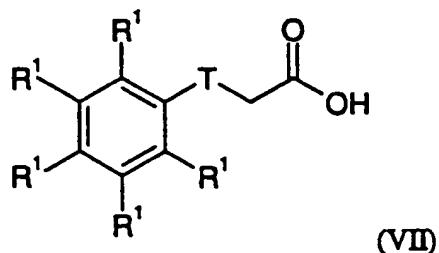
wherein Y represents a bond or a group $(CH_2)_m$ and m and R^4 are as defined in formula (I), in the presence of 1,1-(azodicarbonyl)dipiperidine and tributylphosphine (under conditions of the Mitsunobu reaction: Tetrahedron Lett. (1993), 34, 1639); or

10

(iii) when U represents an oxygen atom and X represents a bond, an oxygen atom or a group $O(CH_2)_m$, NR^5 , NR^5CH_2 , CO , $CONR^5$, SO_2 or SO_2NR^5 reacting a compound of general formula



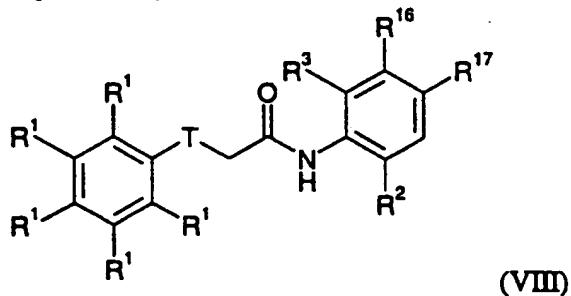
15 wherein one of R^{14} and R^{15} represents a group $-X'-R^4$ and the other of R^{14} and R^{15} represents a hydrogen atom, X' represents a bond, an oxygen atom or a group $O(CH_2)_m$, NR^5 , NR^5CH_2 , CO , $CONR^5$, SO_2 or SO_2NR^5 , and m , R^2 , R^3 , R^4 and R^5 are as defined in formula (I), with a compound of general formula



wherein T and R¹ are as defined in formula (I), in the presence of a coupling reagent such as *isobutylchloroformate* or *bromo-tris-pyrrolidino-phosphonium hexafluorophosphate* and a base (e.g. *diisopropylamine*); or

5

(iv) when U represents an oxygen atom and X represents a bond or a group NR⁵ or NR⁵CH₂, reacting a compound of general formula



wherein one of R¹⁶ and R¹⁷ represents a leaving group, L², such as a halogen atom and the 10 other of R¹⁶ and R¹⁷ represents a hydrogen atom and T, R¹, R² and R³ are as defined in formula (I), with a compound of general formula



wherein Z represents a hydrogen atom or a group NHR⁵ or CH₂NHR⁵ and R⁴ and R⁵ are as defined in formula (I), optionally in the presence of a palladium catalyst (e.g. palladium 15 acetate), a phosphine ligand (e.g. BINAP) and a base (e.g. cesium carbonate); or

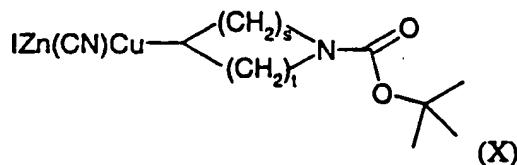
(v) when U represents an oxygen atom and X represents a group CH₂O, reacting a compound of formula (II) as defined in (i) above with a compound of formula (V) as defined in (ii) above wherein Y represents a bond, in the presence of a base (e.g. sodium 20 hydride) or in the presence of a metal salt (e.g. silver trifluoromethanesulfonate); or

(vi) when U represents an oxygen atom and X represents a group CH_2NR^5 , reacting a compound of formula (II) as defined in (i) above with a compound of formula (IX) as defined in (iv) above wherein Z represents a group NHR^5 ; or

5 (vii) when U represents an oxygen atom and X represents a group CH_2OCH_2 , reacting a compound of formula (II) as defined in (i) above with a compound of formula (V) as defined in (ii) above wherein Y represents a group CH_2 , in the presence of a base (e.g. sodium hydride) or in the presence of a metal salt (e.g. silver trifluoromethanesulfonate); or

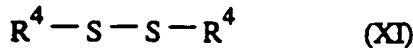
10 (viii) when U represents an oxygen atom and X represents a group $\text{CH}_2\text{NR}^5\text{CH}_2$, reacting a compound of formula (II) as defined in (i) above with a compound of formula (IX) as defined in (iv) above wherein Z represents a group CH_2NHR^5 ; or

15 (ix) when U represents an oxygen atom, X represents a group CH_2 and R^4 represents an unsubstituted 4- to 6-membered saturated heterocyclic ring system containing one nitrogen atom, reacting a compound of formula (II) as defined in (i) above, with a compound of general formula



wherein s and t independently represent 1 or 2; or

(x) when U represents an oxygen atom and X represents a sulfur atom, reacting a compound of formula (VIII) as defined in (iv) above, with n-butyllithium (e.g. at -70 °C) 25 and then with a compound of general formula



wherein R^4 is as defined in formula (I); or

(xi) when U represents an oxygen atom and X represents a CH_2 group, reacting a compound of formula (VIII) as defined in (iv) above, with n-butyllithium (e.g. at -70 °C) and then with a compound of general formula



5 wherein R^4 is as defined in formula (I), followed by a reduction reaction, e.g. with triethylsilane and trifluoroacetic acid or by treatment with methyloxalylchloride and triethylamine followed by tributyltin hydride in the presence of azobisisobutyronitrile; or

10 (xii) when U represents an oxygen atom and X represents a bond, reacting a compound of formula (VIII) as defined in (iv) above, with n-butyllithium (e.g. at -70 °C) and then with a compound of general formula



15 wherein R^4 is as defined in formula (I), followed by a reduction reaction, e.g. with triethylsilane and trifluoroacetic acid or by treatment with methyloxalylchloride and triethylamine followed by tributyltin hydride in the presence of azobisisobutyronitrile; or

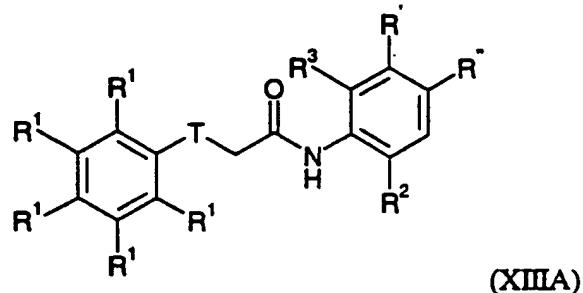
(xiii) when U represents a sulphur atom, reacting a corresponding compound of formula (I) in which U represents an oxygen atom with a thiolating agent (such as Lawesson's reagent) at a temperature, for example, in the range from 0° to 100 °C;

20

(xiv) when U represents a group NH, reacting a corresponding compound of formula (I) in which U represents a sulphur atom with a suitable alkylating agent (e.g. methyl iodide) followed by reaction with ammonium chloride or ammonia;

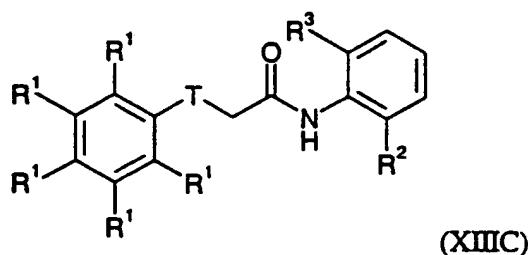
25

(xv) when U represents an oxygen atom and X represents CONR^5 , reacting a compound of general formula



wherein one of R and R' represents a hydrogen atom and the other of R and R' represents a carboxyl group and T, R¹, R² and R³ are as defined in formula (I), with a compound of general formula (XIIIB), R⁴ - NHR⁵, wherein R⁴ and R⁵ are as defined in formula (I); or

(xvi) when U represents an oxygen atom, X represents CH₂ and R⁴ is bonded to X through a nitrogen atom, reacting a compound of general formula



10

wherein T, R¹, R² and R³ are as defined in formula (I), with methane sulphonyl chloride followed by reaction with a compound of general formula (XIIID), R⁴ - H, wherein R⁴ is defined as for R⁴ in formula (I) other than:

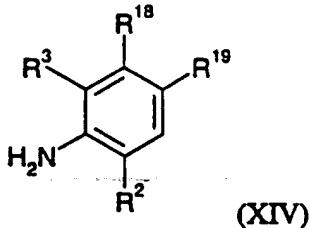
- di(C₁-₂ alkyl)N(CH₂)_t where t is 1 or 2, and
- 15 • 3- to 8-membered saturated carbocyclic ring system substituted by one or more substituents independently selected from NR⁶R⁷, -(CH₂)_rNR⁶R⁷ and -CONR⁶R⁷, the ring system being optionally further substituted by one or more substituents independently selected from fluorine atoms, hydroxyl and C₁-C₆ alkyl;

20 and optionally after (i), (ii), (iii), (iv), (v), (vi), (vii), (viii), (ix), (x), (xi), (xii), (xiii), (xiv), (xv) or (xvi) converting the compound of formula (I) to a further compound of

formula (I) and/or forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

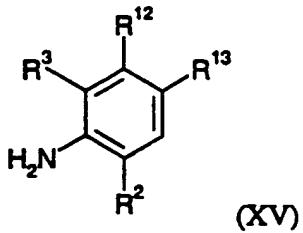
The processes of the invention may conveniently be carried out in a solvent, 5 e.g. an organic solvent such as dichloromethane, tetrahydrofuran, dioxane, xylene or dimethylformamide, at a temperature, e.g. in the range from -78 to 200 °C, preferably in the range from 0 to 150 °C.

Compounds of formula (II) in which L¹ represents, for example, a chlorine atom may 10 be prepared by reacting a compound of general formula



wherein one of R¹⁸ and R¹⁹ represents a hydrogen atom and the other of R¹⁸ and R¹⁹ represents a protected benzylalcohol group (the protecting group used may, for example, be *tert*butyldimethylsilyl) and R² and R³ are as defined in formula (II), with a compound of 15 formula (VII) as defined above, in the presence of a coupling reagent such as isobutylchloroformate or bromo-tris-pyrrolidino-phosphonium hexafluorophosphate and a base (e.g. diisopropylamine), followed by deprotection and reaction with methanesulphonyl chloride in the presence of a base such as diisopropylamine.

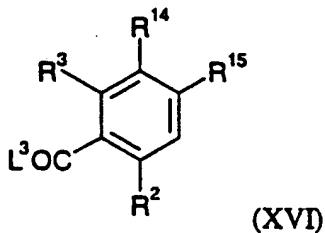
20 Compounds of formula (IV) may be prepared by reacting a compound of general formula



wherein R^2 , R^3 , R^{12} and R^{13} are as defined in formula (IV), with a compound of formula (VII) as defined above, in the presence of a coupling reagent such as *isobutylchloroformate* or *bromo-tris-pyrrolidino-phosphonium hexafluorophosphate* and a base (e.g. *diisopropylamine*)

5

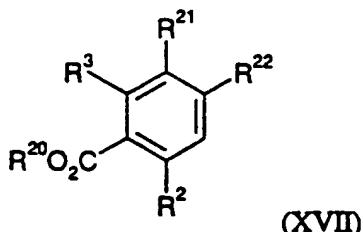
Compounds of formula (VI) may conveniently be prepared by reacting a compound of general formula



wherein L^3 represents a leaving group (e.g. a hydroxyl group) and R^2 , R^3 , R^{14} and R^{15} are as defined in formula (VI), with *diphenylphosphoryl azide* in the presence of a base such as *triethylamine*.

Compounds of formula (XVI) in which X represents a bond, an oxygen atom or a group $O(CH_2)_m$, NR^5 or NR^5CH_2 can be prepared by reacting a compound of general formula

15



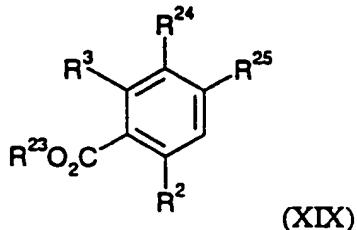
wherein R^{20} represents a hydrogen atom or a C_1 - C_6 alkyl group, one of R^{21} and R^{22} represents a leaving group, L^4 , such as a halogen atom (e.g. bromine or iodine) or a trifluoromethanesulfonate group and the other of R^{21} and R^{22} represents a hydrogen atom, and R^2 and R^3 are as defined in formula (XVI), with a compound of general formula



wherein X'' represents a bond, an oxygen atom or a group $O(CH_2)_m$, NR^5 or NR^5CH_2 and R^4 is as defined in formula (I), in the presence of a palladium catalyst (1996 *J. Am. Chem.*

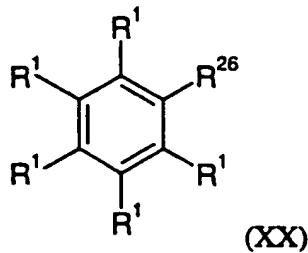
Soc., 7215-6; 1997 *J. Am. Chem. Soc.*, 3395), followed by a hydrolysis reaction (e.g. with sodium hydroxide).

Compounds of formula (XVI) in which X represents CO, CONR⁵, SO₂ or SO₂NR⁵ can be prepared by reacting a compound of general formula



wherein R²³ represents a hydrogen atom or a C₁-C₆ alkyl group, one of R²⁴ and R²⁵ represents a group COL⁵ or SO₂L⁵ and the other of R²⁴ and R²⁵ represents a hydrogen atom, L⁵ represents a leaving group (e.g. a halogen atom) and R² and R³ are as defined in formula (XVI), with a compound of formula (IX) in which Z represents a hydrogen atom or a group NHR⁵, in the presence of a base such as diisopropylethylamine and catalytic *N,N*-dimethylaminopyridine, followed by a hydrolysis reaction (e.g. using sodium hydroxide).

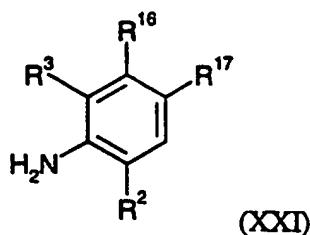
Compounds of formula (VII) may be conveniently prepared by reacting a compound of general formula



wherein R²⁶ represents a hydroxyl group or a protected nitrogen atom (protected by, for example, a *tert*butyloxycarbonyl group) and R¹ is as defined in formula (I), with an alkylating agent (e.g. methyl bromoacetate) followed by a saponification reaction.

20

Compounds of formula (VIII) may be prepared in an analogous manner to compounds of formula (IV) using, instead of the intermediate compound of formula (XV), an intermediate compound of general formula



wherein R^2 , R^3 , R^{16} and R^{17} are as defined in formula (VIII).

Compounds of formula (X) can be prepared as described in *Syn. Lett.* (1998) 379-
5 380.

Compounds of formulae (XIIA) and (XIIIC) may be prepared by processes
analogous to those already described.

10 Compounds of formulae (III), (V), (IX), (XI), (XII), (XIII), (XIIIB), (XIIID), (XIV),
(XV), (XVII), (XVIII), (XIX), (XX) and, (XXI) are either commercially available, are well
known in the literature or may be prepared easily using known techniques.

15 Compounds of formula (I) can be converted into further compounds of formula (I)
using standard procedures. For example, compounds of formula (I) in which one of R^2 and
 R^3 represents a nitro group can be converted to compounds of formula (I) in which one of
 R^2 and R^3 represents an amino group by reduction using iron powder and ammonium
chloride in ethanol/water under reflux conditions. The latter compounds can in turn be
converted into compounds of formula (I) in which one of R^2 and R^3 represents a halogen
20 atom, e.g. chlorine, by diazotization (e.g. with sodium nitrite) and reaction with copper
chloride. Compounds of formula (I) in which R^6 or R^7 represents a hydrogen atom can be
converted to compounds of formula (I) in which R^6 or R^7 represents a C_1 - C_6 alkyl,
 C_3 - C_8 cycloalkyl or a 3- to 8-membered saturated heterocyclic ring by standard chemical
procedures.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve at a certain stage the removal 5 of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, 10 Wiley-Interscience (1991).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, 15 methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the 20 compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compounds of the present invention are advantageous in that they possess pharmacological activity. They are therefore indicated as pharmaceuticals for use in the 25 treatment of rheumatoid arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma, chronic obstructive pulmonary disease (COPD), hyperresponsiveness of the airway, septic shock, glomerulonephritis, irritable bowel disease, Crohn's disease, ulcerative colitis, atherosclerosis, growth and metastases of malignant cells, myoblastic leukaemia, diabetes, Alzheimer's disease, meningitis, osteoporosis, burn injury, ischaemic heart disease, stroke 30 and varicose veins.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

5

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

10

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

15

The invention further provides a method of effecting immunosuppression (e.g. in the treatment of rheumatoid arthritis, irritable bowel disease, atherosclerosis or psoriasis) which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

20

The invention also provides a method of treating an obstructive airways disease (e.g. asthma or COPD) which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

25

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I)/salt/solvate (active ingredient) may be in the range from 0.001 mg/kg to 30 mg/kg.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

5 Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

10

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

15

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

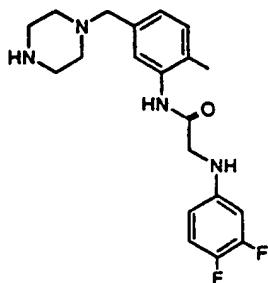
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The pharmaceutical composition of the invention may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by 25 parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The present invention will now be further explained by reference to the following illustrative examples.

Example 1

5 **2-(3,4-Difluorophenylamino)-N-(2-methyl-5-piperazin-1-ylmethyl-phenyl)-acetamide, trihydrochloride**



a) **[*tert*-Butoxycarbonyl-(3,4-difluorophenyl)-amino]-acetic acid methyl ester**

To a solution of (3,4-difluorophenyl)-carbamic acid *tert*-butyl ester (Tetrahedron, 1992, 48(35), 7373) (15.1 g) in tetrahydrofuran (120 ml) at 0° C was added potassium *tert*-butoxide (94 ml of a 1.0 M solution in tetrahydrofuran) dropwise. After stirring for 2hr methyl bromoacetate (9.1 ml) was added dropwise and ice-bath removed and reaction mixture stirred at room temperature overnight. Reaction mixture concentrated under reduced pressure, diluted with ethyl acetate and washed with water and brine, dried (Na₂SO₄) and concentrated to leave the sub-title compound as a brown oil (18.0 g).

¹H NMR (DMSO-d₆) δ 7.43-7.12 (3H, m), 4.33 (2H, s), 3.67 (3H, s), 1.37 (9H, s).

b) **[*tert*-Butoxycarbonyl-(3,4-difluorophenyl)-amino]-acetic acid**

To a solution of [*tert*-butoxycarbonyl-(3,4-difluorophenyl)-amino]-acetic acid methyl ester (14.7 g) in tetrahydrofuran (100 ml) was added water (100 ml) and lithium hydroxide monohydrate (6.2 g) and reaction mixture stirred at room temperature over-night before removal of tetrahydrofuran at reduced pressure. Residue was acidified to pH 4 by addition of KHSO₄ (10% solution in water) and extracted with ethyl acetate. Organic extracts

combined, dried (Na_2SO_4) and concentrated to leave the sub-title compound as a gum (12.3 g).

5 ^1H NMR (DMSO-d₆) δ 12.82 (1H, s), 7.37 (2H, m), 7.14 (1H, m), 4.22 (2H, s),
1.38 (9H, s).

c) 4-(4-Methyl-3-nitro-benzyl)-piperazine-1-carboxylic acid *tert*-butyl ester

To a solution of 4-chloromethyl-1-methyl-2-nitro-benzene (2 g) and triethylamine (3 ml) in DMF (10 ml) was added piperazine-1-carboxylic acid *tert*-butyl ester (2.01 g) and 10 the stirred reaction heated at 78 °C for 15hr. After cooling to room temperature, the reaction was poured into ethyl acetate / water and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with water, aqueous KHSO_4 , aqueous K_2CO_3 and brine, dried (Na_2SO_4) and concentrated to leave the sub-title compound as a brown oil (3.5 g).

15 ^1H NMR (DMSO-d₆) δ 7.89 (1H, d), 7.56 (1H, dd), 7.46 (1H, d), 3.55 (2H, s), 3.30 (7H, m), 2.33 (4H, m), 1.39 (9H, s).

d) 4-(3-Amino-4-methyl-benzyl)-piperazine-1-carboxylic acid *tert*-butyl ester

20 To crude 4-(4-methyl-3-nitro-benzyl)-piperazine-1-carboxylic acid *tert*-butyl ester (3.5 g) in EtOH / water (60 ml, 1:1) was added iron powder (4 g) and solid NH_4Cl (4 g) and the mixture heated to reflux temperature for 1.5hr. After cooling to room temperature the reaction was filtered through Celite and the filter cake washed with further EtOH. The 25 majority of the solvent was removed *in vacuo* before addition of ethyl acetate and aqueous K_2CO_3 . The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated, to leave an oil that was triturated with isohexanes to afford a pale brown solid (3 g).

30 ^1H NMR (DMSO-d₆) δ 6.83 (1H, d), 6.55 (1H, d), 6.38 (1H, dd), 4.75 (2H, s),
3.28 (4H, m), 2.26 (4H, t), 2.01 (3H, s), 1.38 (9H, s).

e) 4-(3-{2-[*tert*-Butoxycarbonyl-(3,4-difluoro-phenyl)-amino]-acetylamino}-4-methyl-benzyl)-piperazine-1-carboxylic acid *tert*-butyl ester.

To a solution of [*tert*-butoxycarbonyl-(3,4-difluorophenyl)-amino]-acetic acid (0.200 g) in tetrahydrofuran (2 ml) at 0 °C was added triethylamine (110 ul) followed by dropwise addition of isobutylchloroformate (100 ul). After stirring for 1hr, triethylamine (150 ul) was added followed by 4-(3-amino-4-methyl-benzyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.234 g) in tetrahydrofuran (2 ml), and the reaction warmed to room temperature and then heated at 58 °C overnight. After cooling to room temperature, the reaction mixture was filtered through Celite, the filtrate collected and the solvent removed *in vacuo*. Purification by NPHPLC (0-5% MeOH in CH₂Cl₂) afforded the sub-title compound as a pale yellow solid (0.300 g).

¹H NMR (DMSO-d₆) δ 9.43 (1H, brs), 7.42 (2H, m), 7.35 (1H, s), 7.21 (1H, m), 7.15 (1H, d, J = 7.6 Hz), 7.01 (1H, d, J = 7.6 Hz), 4.38 (2H, s), 3.42 (2H, s), 3.29 (4H, m), 2.29 (4H, m), 2.15 (3H, s), 1.39 (9H, s), 1.38 (9H, s).

f) 2-(3,4-Difluorophenylamino)-N-(2-methyl-5-piperazin-1-ylmethyl-phenyl)-acetamide trihydrochloride

To a solution of 4-(3-{2-[*tert*-Butoxycarbonyl-(3,4-difluoro-phenyl)-amino]-acetylamino}-4-methyl-benzyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.100 g) in MeOH (3 ml) was added HCl (2ml of 4M solution in dioxane). After standing for several hours, a solid was filtered off, washed with acetone and dried *in vacuo*. The solid was re-suspended in acetone, sonicated for 5 min filtered and dried to afford the title compound (0.043g, 51%).

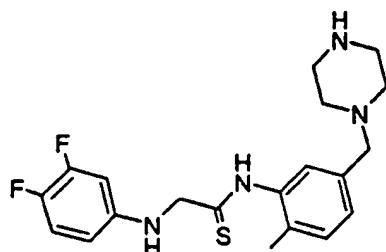
Melting point: 232-248 (dec) °C.

MS (ESI) 375 (M+H)⁺ for free base.

¹H NMR (DMSO-d₆) δ 9.54 (3H, brs), 7.68 (1H, m), 7.37 (1H, d), 7.29 (1H, d), 7.16 (1H, dd), 6.61 (1H, ddd), 6.41 (1H, m), 4.33 (2H, brs), 3.92 (2H, s), 3.43-3.11 (10 H, m), 2.17 (3H, s).

5 **Example 2**

2-(3,4-Difluoro-phenylamino)-N-(2-methyl-5-piperazin-1-ylmethyl-phenyl)-thioacetamide



To a solution of 4-(3-{2-[*tert*-butoxycarbonyl-(3,4-difluoro-phenyl)-amino]-10 acetylamino}-4-methyl-benzyl)-piperazine-1-carboxylic acid *tert*-butyl ester (160 mg) in toluene (4 ml) was added Lawesson's reagent (100mg) and the reaction heated at 100 °C for 2.5 hr. After cooling to room temperature, the solvent was removed *in vacuo* to afford a yellow powder. Purification by NPHPLC (0-5% MeOH in CH₂Cl₂) afforded 4-(3-{2-[*tert*-butoxycarbonyl-(3,4-difluoro-phenyl)-amino]-15 thioacetylamino}-4-methyl-benzyl)-piperazine-1-carboxylic acid *tert*-butyl ester (120 mg). This was taken up in CH₂Cl₂ (1 ml) and trifluoroacetic acid (0.63 ml) added. After 2hr stirring the reaction was poured into aqueous K₂CO₃ and the organic layer was separated, washed with aqueous K₂CO₃ and brine, dried (Na₂SO₄) and concentrated to leave yellow crystals. They were purified further by reverse phase HPLC to afford the title compound (14 mg).

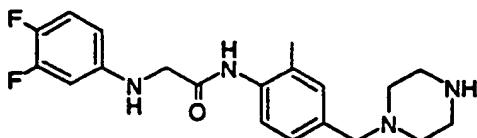
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Melting point: 72-82 (dec) °C.

MS (ESI) 391 (M+H)⁺ for free base.

¹H NMR (DMSO-d₆) δ 7.25 (2H, m), 7.18 (2H, m), 6.63 (2H, m), 6.45 (1H, d), 4.26 (2H, d), 3.57 (4H, m), 2.75 (4H, t), 2.35 (4H, brs), 2.06 (3H, s), (no thioamide proton

25 observed).

Example 3**2-(3,4-Difluoro-phenylamino)-N-(2-methyl-4-piperazin-1-ylmethyl-phenyl)-acetamide, trihydrochloride**5 a) **4-(*tert*-Butyl-dimethyl-silyloxy)methyl)-2-methyl-phenylamine**

To a solution of (3-methyl-4-nitro-phenyl)-methanol (1.22 g) and imidazole (0.99 g) in *N,N*-dimethylformamide (5 ml) was added *tert*-butyldimethylsilyl chloride (0.99g) and the solution stirred for 5 hours before being poured into ethyl acetate / water and the organic layer separated, washed with water and brine, dried (Na_2SO_4) and concentrated.

10 Purification of the residue by silica gel chromatography (eluting with 10% ethyl acetate in iso-hexane) gave 1.5 g of a pale brown oil. This was dissolved in ethanol (8 ml), cooled to 0 °C, and aqueous CuSO_4 (0.5 ml of a 2M solution) added. Sodium borohydride (1.32 g) was added in small portions and the reaction was warmed to room temperature. Further portions of aqueous CuSO_4 (0.5 ml) were added each hour until reduction was complete.

15 Ethyl acetate was added, and the organic layer separated, washed with water and brine, dried (Na_2SO_4) and concentrated, to leave the sub-title compound as an oil (1.3 g).

¹H NMR (DMSO-d₆) δ 6.81 (2H, m), 6.54 (1H, d), 4.73 (2H, brs), 4.48 (2H, s), 2.03 (3H, s), 0.97 (9H, s), 0.04 (6H, s).

20

b) **(3,4-Difluoro-phenyl)-[(4-hydroxymethyl-2-methyl-phenylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester**

To a solution of [*tert*-butoxycarbonyl-(3,4-difluorophenyl)-amino]-acetic acid (5.74 g) in tetrahydrofuran (40 ml) at 0 °C was added triethylamine (3.2 ml) followed by 25 isobutylchloroformate (2.9 ml) dropwise. After stirring for 1hr, triethylamine (3.2 ml) was added followed by 4-(*tert*-butyl-dimethyl-silyloxy)methyl)-2-methyl-phenylamine (5.0 g) in tetrahydrofuran (3 ml), and the reaction warmed to room temperature and then heated at 58 °C overnight. After cooling to 0 °C, tetrabutylammonium fluoride (7.6 ml of a 1M

solution in tetrahydrofuran) was added dropwise and the reaction warmed to room temperature. After 3 hrs, the solution was poured into ethyl acetate / water and the organic layer separated, washed with KHSO_4 (10% solution in water), water and brine, dried (Na_2SO_4) and concentrated. Purification of the residue by silica gel chromatography (eluting with 3% methanol in dichloromethane) gave an orange solid. Recrystallisation from 2-propanol / isohexane gave the sub-title compound as white crystals (2.8 g).

Melting point: 134-136 °C.

MS (ESI) 307 ($\text{M}+\text{H}$)⁺

10 ^1H NMR (DMSO-d₆) δ 9.41 (1H, s), 7.49 - 7.39 (3H, m), 7.23 (1H, m), 7.12 (2H, m), 5.11 (1H, t), 4.43 (2H, d), 4.37 (2H, s), 2.16 (3H, s), 1.39 (9H, s).

c) 2-(3,4-Difluoro-phenylamino)-N-(2-methyl-4-piperazin-1-ylmethyl-phenyl)-acetamide trihydrochloride

15 To a solution of (3,4-difluoro-phenyl)-[(4-hydroxymethyl-2-methyl-phenylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester (0.100 g) in dry tetrahydrofuran (1 ml) was added *N,N*-diisopropylethylamine (0.17 ml) followed by methanesulfonyl chloride (0.04 ml) in a single portion. After 2 hr piperazine-1-carboxylic acid *tert*-butyl ester (0.137 g) was added, and the reaction heated at 70 °C for 10 hrs. After cooling to 20 room temperature, the reaction was poured into ethyl acetate / water. The organic layer was separated, washed with water, aqueous KHSO_4 and aqueous NaHCO_3 . The organic layer was dried (Na_2SO_4) and concentrated. Purification by NPHPLC (eluting with 0-25% methanol in dichloromethane) gave a brown solid (0.120 g). This was taken up in methanol (3 ml) and HCl (1 ml of a 4M solution in dioxane) added. After 24 hrs, the 25 resulting crystals were filtered off, washed with acetone and dried *in vacuo* to give the title compound as a white powder (0.060 g).

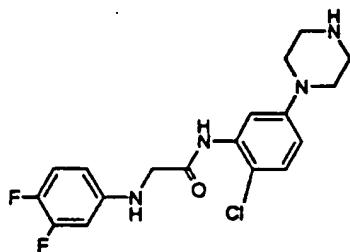
Melting Point: 278 (dec) °C.

MS (ESI) 375 ($\text{M}+\text{H}$)⁺ for free base

¹H NMR (DMSO-d₆) δ 9.50 (3H, s), 7.58 (1H, d), 7.46 (1H, s), 7.42 (1H, d), 7.16 (1H, q), 6.61 (1H, ddd), 6.40 (1H, d), 4.44 (3H, s), 4.31 (2H, s), 3.57 (6H, s), 3.19 (2H, s), 2.16 (3H, s).

5 **Example 4**

N-(2-Chloro-5-piperazin-1-yl-phenyl)-2-(3,4-difluoro-phenylamino)-acetamide, trihydrochloride



a) **4-(4-Chloro-3-ethoxycarbonyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester**

Piperazine-1-carboxylic acid *tert*-butyl ester (106 mg), 3-bromo-6-chlorobenzoic acid ethyl ester (125 mg), cesium carbonate (220 mg), palladium acetate (5 mg) and *R*-BINAP (22 mg) were combined in toluene (2 ml) and heated at 100°C in a sealed vessel for 48hr. The cooled reaction was loaded onto a silica column and eluted with *iso*-hexane / ethyl acetate (4:1) to give the subtitle product (170 mg).

MS (APCI+ve) 269 /271 (M+H-(*tert*-butyloxycarbonyl))⁺

¹H NMR (CDCl₃) δ 7.28-7.31 (2H, m), 6.94 (1H, dd), 4.39 (2H, q), 3.58 (4H, t), 3.13 (4H, t), 1.48 (9H, s), 1.40 (3H, t).

20

b) **5-(4-*tert*-Butoxycarbonyl-piperazin-1-yl)-2-chloro-benzoic acid, lithium salt**

To a solution of 4-(4-chloro-3-ethoxycarbonyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (2.2 g) in tetrahydrofuran (10 ml) and water (5 ml) was added lithium hydroxide monohydrate (370 mg). Reaction mixture was stirred at room temperature for 48hr before concentration at reduced pressure to give the subtitle product (2.1 g).

MS (APCI+ve) 340 /342 (M+H)⁺ for free acid

¹H NMR (D₂O) δ 7.40 (1H, d), 7.06-7.11 (2H, m), 3.65 (4H, t), 3.17 (4H, t), 1.50 (1H, s).

c) **4-(3-Amino-4-chloro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester**

To a solution of 5-(4-*tert*-butoxycarbonyl-piperazin-1-yl)-2-chloro-benzoic acid lithium salt (2.1 g) in *N,N*-dimethylformamide (50 ml) was added diphenyl phosphorylazide (1.4 ml) and reaction mixture stirred at ambient temperature for 1 hour. Water (30 ml) was added and the reaction mixture heated to 60°C for 2 hours. After cooling to room temperature, the reaction was poured into ethyl acetate / water, the organic layer separated, washed with water, aqueous NaHCO₃ and brine. The organic layer was dried (MgSO₄) and concentrated. Purification of the residue by silica gel chromatography (eluting ethyl acetate / *iso*-hexane (1:3 to 1:1) gave the subtitle product (1.5 g).

MS (APCI+ve) 312 / 314 (M+H)⁺

¹H NMR (DMSO-d₆) δ 6.98 (1H, d), 6.35 (1H, d), 6.19 (1H, dd), 5.12 (2H, s), 3.44 (4H, t), 2.98 (4H, t), 1.41 (9H, s).

d) **4-[4-Chloro-3-(2-chloro-acetylamino)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester**

To a solution of 4-(3-amino-4-chloro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (500mg) and *N,N*-diisopropylethylamine (0.8ml) in tetrahydrofuran (20ml) cooled to 0°C was added 2-chloroacetyl chloride (0.2ml). After 2hrs, the reaction was poured into ethyl acetate / water. The organic layer was separated, washed with water, aqueous NaHCO₃ and brine, dried (MgSO₄) and concentrated. Purification of the residue by silica gel chromatography (eluting ethyl acetate / *iso*-hexane (1:3 to 1:2) gave the sub-title product (0.5g).

MS (APCI+ve) 388 / 390 /392 (M+H)⁺

¹H NMR (CDCl₃) δ 8.81 (1H, brs), 8.05 (1H, d), 7.24 (1H, d), 6.63 (1H, dd), 4.22 (2H, s),

3.56 (4H, t), 3.14 (4H, t), 1.48 (9H, s).

e) 4-{4-Chloro-3-[2-(3,4-difluoro-phenylamino)-acetylamino]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester

Potassium iodide (10mg), 3,4-difluoroaniline (0.4ml), *N,N*-diisopropyl ethylamine (0.9ml) and 4-[4-chloro-3-(2-chloro-acetylamino)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (500mg) were combined in *N,N*-dimethylformamide (10 ml) and heated at 90°C for 24hr. After cooling to room temperature, the reaction was poured into ethyl acetate / water. The organic layer was separated, washed with water (x3) and brine, dried (MgSO₄) and concentrated. Purification of the residue by silica gel chromatography (eluting ethyl acetate / *iso*-hexane (1:2 to 1:1) gave the subtitle product (360 mg).

MS (APCI+ve) 481 / 483 (M+H)⁺

¹H NMR (CDCl₃) δ 9.01 (1H, s), 8.13 (1H, d), 7.18 (1H, d), 7.00 (1H, q), 6.59 (1H, dd), 6.54 (1H, ddd), 6.38 (1H, brd), 4.38 (1H, t), 3.91 (2H, d), 3.57 (4H, t), 3.15 (4H, t), 1.48 (9H, s).

f) 4 *N*-(2-Chloro-5-piperazin-1-yl-phenyl)-2-(3,4-difluoro-phenylamino)-acetamide

4M Hydrochloric acid in dioxane (3 ml) was added to a solution of 4-[4-chloro-3-[2-(3,4-difluoro-phenylamino)-acetylamino]-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (340 mg) in ether (20 ml). After 24 hours the precipitated solid was collected by filtration and washed successively with dichloromethane, acetonitrile, ethyl acetate, then recrystallised from ethanol to give the title product as the dihydrochloride (60 mg).

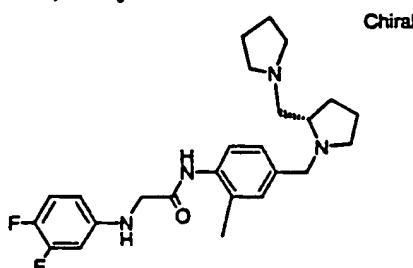
Melting point: 240°C (dec).

MS (APCI+ve) 381 / 383 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.44 (1H, s), 9.21 (2H, brs), 7.59 (1H, d), 7.33 (1H, d), 7.15 (1H, q), 6.82 (1H, dd), 6.63 (1H, ddd), 6.60 (2H, brs), 6.40 (1H, t), 3.91 (2H, s), 3.34 (4H, t), 3.20 (4H, t).

Example 5

(S)-2-(3,4-Difluoro-phenylamino)-N-[2-methyl-4-(2-pyrrolidin-1-ylmethyl-pyrrolidin-1-ylmethyl)-phenyl]-acetamide, trihydrochloride



5 To a solution of (3,4-difluoro-phenyl)-[(4-hydroxymethyl-2-methyl-phenylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester (0.200 g) from Example 3b) in dry 1-methyl-2-pyrrolidinone (2 ml) was added *N,N*-diisopropylethylamine (0.52 ml) followed by methanesulfonyl chloride (0.16 ml) in a single portion. After 3 hours the reaction was poured into ethyl acetate / water. The organic layer was separated and washed with aqueous KHSO_4 , aqueous NaHCO_3 and brine. The organic layer was dried (Na_2SO_4) and concentrated to a pale red oil which was dissolved in 1-methyl-2-pyrrolidinone (8 ml) and *N,N*-diisopropylethylamine (0.52 ml) and (S)-(+)-1-(2-pyrrolidinylmethyl)-pyrrolidine (0.41 ml) were added, and the reaction heated at 95 °C overnight. After cooling to room temperature, the reaction was poured into ethyl acetate / water. The organic layer was separated and washed with aqueous KHSO_4 , aqueous K_2CO_3 and brine, dried (Na_2SO_4) and concentrated to a pale red oil. Purification by NPHPLC (eluting with 0-25% methanol in dichloromethane) gave a white solid which was dissolved in methanol (2 ml) and HCl (1 ml of a 4M solution in dioxane) added. After 2 hours, the solvent was removed and the residue recrystallised from isopropanol / acetonitrile to give the title compound as a white powder (0.071 g).

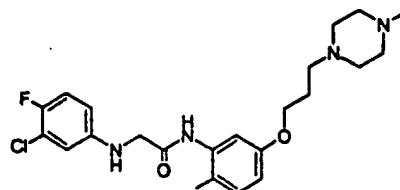
Melting Point: 178 (dec) °C.

MS (ESI+ve) 443 (M+H)⁺ for free base

¹H NMR (DMSO-d₆) δ 9.49 (1H, s), 7.55 (2H, m), 7.47 (1H, d), 7.16 (1H, q), 6.10 (1H, ddd), 6.40 (1H, d), 4.68 (1H, d), 4.13 (1H, dd), 3.92 (4H, m), 3.58 (3H, m), 3.20 (1H, m), 3.13 (1H, m), 2.98 (2H, m), 2.17 (3H, s), 2.00 (8H, m), NH's not observed.

5 **Example 6**

2-(3-Chloro-4-fluorophenylamino)-N-{2-methyl-5-[3-(4-methylpiperazin-1-yl)-propoxyl]phenyl}acetamide



a) **2-Chloro-N-(5-methoxy-2-methylphenyl)-acetamide**

10 To a solution of 2-methyl-5-methoxyaniline (4.7 g) in tetrahydrofuran (50 ml), under nitrogen, was added diisopropylethylamine (12.6 ml) followed by dropwise addition of chloroacetyl chloride (2.7 ml) and the mixture stirred under nitrogen for 27 hours. The solution was poured into 2M aqueous hydrochloric acid (150 ml), extracted into diethyl ether (3 x 150 ml), washed with brine, dried (MgSO₄), and concentrated to give the sub-
15 title compound as a brown oil (5.15 g).

¹H NMR (CDCl₃) δ 8.24 (1H, s), 7.64 - 7.63 (1H, d), 7.11 - 7.08 (1H, d), 6.70 - 6.66 (1H, dd), 4.23 (2H, s), 3.80 (3H, s), 2.24 (3H, s).

20 b) **2-(3-Chloro-4-fluorophenylamino)-N-(5-methoxy-2-methylphenyl)-acetamide.**
2-Chloro-N-(5-methoxy-2-methylphenyl)-acetamide (3 g), 3-chloro-4-fluoroaniline (7.56 g), diisopropylethylamine (13.8 ml), potassium iodide (0.005 g) and anhydrous tetrahydrofuran (20 ml) were heated together at 105 °C in a sealed tube for 19 hours. The mixture was then cooled and concentrated. Purification of the residue by silica gel
25 chromatography (eluting with 1 : 1 iso-hexane / ethyl acetate) gave the sub-title compound (3.93 g).

MS (APCI +ve) 323 (M+H)⁺

¹H NMR (CDCl₃) δ 8.42 (1H, s), 7.71 - 7.70 (1H, d), 7.04 - 6.89 (2H, m), 6.76 - 6.47 (3H, m), 4.38 (1H, t), 3.92 - 3.90 (2H, d), 3.80 (3H, s), 2.00 (3H, s).

5 c) 2-(3-Chloro-4-fluorophenylamino)-N-(5-hydroxy-2-methylphenyl)-acetamide

To a solution of 2-(3-chloro-4-fluorophenylamino)-N-(5-methoxy-2-methylphenyl)-acetamide (3.93 g) in anhydrous dichloromethane (450 ml) was stirred under nitrogen at -78 °C was added a solution of boron tribromide (1M in dichloromethane, 95 ml) dropwise. The mixture was then allowed to warm to room temperature and stirred under nitrogen for 20 hours before being poured into ice/water (1 l), stirred vigorously for 1 hour and extracted into ethyl acetate (3 x 500 ml), dried (MgSO₄) and concentrated. Purification of the residue by silica gel chromatography (eluting with 3% methanol in dichloromethane) gave the sub-title compound (2.65 g).

15 MS (APCI +ve) 309 (M+H)⁺

¹H NMR (DMSO-d6) δ 9.18 (1H, s), 9.14 (1H, s), 7.18 - 7.12 (1H, t), 7.01 (1H, s), 6.96 - 6.94 (1H, d), 6.73 - 6.70 (1H, m), 6.61 - 6.57 (1H, m), 6.49 - 6.46 (1H, d), 6.35 - 6.31 (1H, t), 3.88 - 3.86 (2H, d), 2.00 (3H, s).

20 d) 2-(3-Chloro-4-fluorophenylamino)-N-[2-methyl-5-[3-(4-methylpiperazin-1-yl)-propoxyl]phenyl]acetamide

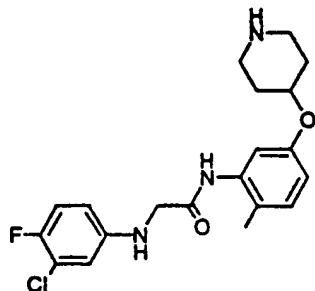
To a solution of 2-(3-chloro-4-fluoro-phenylamino)-N-(5-hydroxy-2-methyl-phenyl)-acetamide (0.400 g) and 4-methyl-1-piperazinepropanol (0.270 g) in tetrahydrofuran (20 ml) under a nitrogen atmosphere was added tributylphosphine (0.64 ml) and 1,1'-(azodicarbonyl)dipiperidine (0.656 g) and the mixture stirred at ambient temperature for 20 hours. The reaction mixture was poured into diethylether and filtered through Celite. After concentration, the residue was purified by NPHPLC (eluting with 75% ethanol in dichloromethane) to afford the title compound (0.334 g).

30 MS (APCI+ve) 449 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.24 (1H, s), 7.18 - 7.05 (3H, m), 6.74 - 6.56 (3H, m), 6.35 - 6.31 (1H, t), 3.94 - 3.87 (4H, q), 2.49 - 2.26 (10H, m), 2.18 (3H, s), 2.05 (3H, s), 1.87 - 1.78 (2H, quintet).

5 **Example 7**

(+/-)-2-(3-Chloro-4-fluoro-phenylamino)-N-[2-methyl-5-(piperidin-4-yloxy)-phenyl]-acetamide, dihydrochloride



To a solution of 2-(3-chloro-4-fluoro-phenylamino)-N-(5-hydroxy-2-methyl-phenyl)acetamide (0.10 g) and 4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (Synlett. 1998, 4, 379) (0.163 g) in tetrahydrofuran (3 ml) was added tributylphosphine (0.20 ml) and 1,1'-(azodicarbonyl)dipiperidine (0.204 g) and the mixture heated at 60 °C for 3 hours. Further 4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (0.163 g), tributylphosphine (0.20 ml) and 1,1'-(azodicarbonyl)dipiperidine (0.204 g) were then added and the heating continued. After 3 hours, the reaction was cooled, poured into diethyl ether and filtered through Celite. After concentration, the residue was purified by NPHPLC (eluting with 0-5% ethanol in dichloromethane) to afford a white solid that was dissolved in methanol (3 ml) and HCl (2 ml of a 4M solution in dioxane) added. After 24 hours, the crystals were filtered off, washed with dichloromethane and dried *in vacuo* to give the title compound as a white powder (0.080 g).

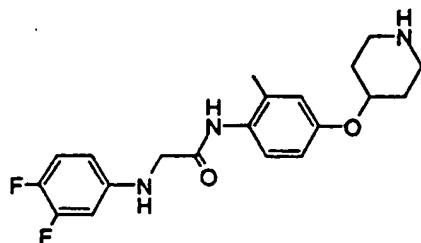
Melting Point: 179 (dec) °C.

MS (APCI+ve) 392/394 (M+H)⁺ for free base

¹H NMR (DMSO-d₆) δ 9.33 (1H, s), 8.90 (1H, brs), 8.85 (1H, brs), 7.18-7.09 (3H, m), 6.74 (2H, m), 6.60 (1H, m), 5.53 (2H, brs), 4.55 (1H, m), 3.90 (2H, s), 3.17 (2H, m), 3.05 (2H, m), 2.06 (3H, s), 2.06 (2H, m), 1.80 (2H, m).

5 **Example 8**

2-(3,4-Difluoro-phenylamino)-N-[2-methyl-4-(piperidin-4-yloxy)-phenyl]-acetamide, dihydrochloride



a) **4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methyl-phenylamine**

10 To a solution of 4-amino-2-methyl-phenol (1 g) and imidazole (1.66 g) in tetrahydrofuran (10 ml) was added *tert*-butyldimethylsilyl chloride (1.1 g) and the solution stirred for 15 hours before being poured into ethyl acetate / water and the organic layer separated, washed with water, aqueous K₂CO₃ and brine, dried (Na₂SO₄) and concentrated to a red oil. Purification of the residue by silica gel chromatography (eluting with 50% ethyl acetate in isohexane) gave a pale red oil (1.5 g) which was used without further 15 purification.

20 ¹H NMR (DMSO-d₆) δ 6.39-6.28 (3H, m), 4.27 (2H, s), 1.89 (3H, s), 0.82 (9H, s), 0.00 (6H, s).

b) **(3,4-Difluoro-phenyl)-[(4-hydroxy-2-methyl-phenylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester**

25 Prepared according to Example 3b) using [*tert*-butoxycarbonyl-(3,4-difluorophenyl)-amino]-acetic acid (1.82 g) (from Example 1b) and 4-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-phenylamine (1.5 g). Purification by silica gel chromatography (eluting with 30%

ethyl acetate in isohexane) followed by trituration with diethyl ether gave the sub-title compound as a white powder (1.47 g).

5 ^1H NMR (DMSO-d₆) δ 9.25 (1H, s), 9.22 (1H, s), 7.44 (2H, m), 7.21 (1H, m), 7.03 (1H, d),
 6.56 (2H, m), 4.32 (2H, s), 2.08 (3H, s), 1.39 (9H, s).

c) **2-(3,4-Difluoro-phenylamino)-N-[2-methyl-4-(piperidin-4-yloxy)-phenyl]-acetamide, dihydrochloride**

10 Prepared according to Example 7 using (3,4-difluoro-phenyl)-[(4-hydroxy-2-methyl-phenylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester (100 mg) to leave the title compound as a white powder (0.033 g).

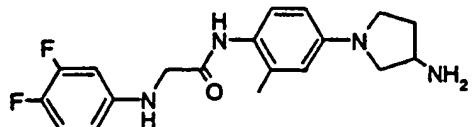
Melting Point: 210 (dec) °C.

MS (APCI+ve) 376 (M+H)⁺ for free base

15 ^1H NMR (DMSO-d₆) δ 9.33 (1H, s), 8.68 (2H, brs), 7.23 (1H, m), 7.15 (1H, q), 6.81 (2H, m), 6.59 (1H, ddd), 6.41 (1H, m), 6.10 (2H, brs), 4.58 (1H, m), 3.85 (2H, s), 3.20 (2H, m), 3.05 (2H, m), 2.08 (3H, s), 2.06 (2H, m), 1.82 (2H, m).

Example 9

20 **(\pm)-N-[5-(3-Amino-pyrrolidin-1-yl)-2-methyl-phenyl]-2-(3,4-difluoro-phenylamino)-acetamide, trihydrochloride**



a) (\pm)-[1-(3-Methyl-4-nitrophenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester
 4-Fluoro-2-methyl-1-nitrobenzene (1 g), pyrrolidin-3-ylcarbamic acid *tert*-butyl ester
 25 (1.2 g), potassium carbonate (1.79 g) and dimethyl sulfoxide (10 ml) were heated together
 at 80 °C under nitrogen for 15 hours. The mixture was cooled, diluted with ethyl acetate
 (200 ml), washed with 2M aqueous hydrochloric acid (200 ml), dried (MgSO₄), and

concentrated. Purification of the residue by silica gel chromatography (eluting with 20% ethyl acetate in isohexane) gave the sub-title compound (1.744 g) as a yellow solid.

15 ¹H NMR (DMSO-d₆) δ 8.03 - 8.00 (1H, d), 7.28 - 7.21 (1H, br d), 6.51 - 6.47 (2H, m),
5 4.20 - 4.12 (1H, br m), 3.61 - 3.16 (4H, m), 2.56 (3H, s), 2.20 - 2.08 (1H, m), 1.98 - 1.85
(1H, m), 1.39 (9H, s).

10 b) (±)-[1-(4-Amino-3-methylphenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester
[1-(3-Methyl-4-nitrophenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (1.744 g).
iron powder (1.52 g), ammonium chloride (1.45 g), ethanol (50 ml) and water (50 ml) were
heated to reflux temperature under nitrogen for 2 hours. The mixture was cooled and the
iron filtered off. Water (200 ml) was added to the residue and the product extracted into
ethyl acetate (3 x 200 ml), dried (MgSO₄), and concentrated to give the sub-title compound
(1.56 g).

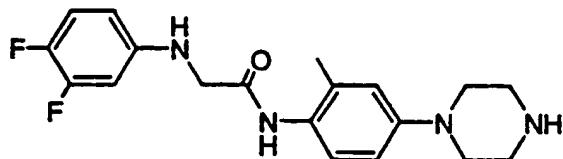
15

¹H NMR (CDCl₃) δ 6.65 (1H, br s), 6.38 (2H, br m), 4.80 (1H, m), 4.33 (2H, br m),
3.60 - 2.80 (5H, m), 2.31 - 2.17 (4H, m), 1.92 - 1.82 (1H, m), 1.45 (9H, br s).

20 c) (±)-N-[5-(3-Amino-pyrrolidin-1-yl)-2-methyl-phenyl]-2-(3,4-difluoro-
phenylamino)-acetamide, trihydrochloride
Prepared according to the procedures for Examples 4d), 4e) & 4f), without
characterisation of intermediates, [1-(3-Amino-4-methyl-phenyl)-pyrrolidin-3-yl]-carbamic
acid *tert*-butyl ester (750mg) gave the title compound (200mg) as the trihydrochloride.

25 MS (APCI+ve) 361 (M+H)⁺ for free base

¹H NMR (DMSO-d₆) δ 9.22 (1H, s), 8.33 (2H, brs), 7.10-7.20 (2H, m), 6.60 (1H, ddd),
6.37-6.40 (3H, m), 5.70 (2H, brs), 3.91 (1H, brs), 3.82 (2H, s), 3.40-3.51 (2H, m),
3.20-3.30 (2H, m), 2.24-2.36 (2H, m), 2.07 (3H, s).

Example 10**2-(3,4-Difluoro-phenylamino)-N-(2-methyl-5-piperazin-1-yl-phenyl)-acetamide, trihydrochloride**

5 a) **4-(3-Methyl-4-nitrophenyl)-piperazine-1-carboxylic acid *tert*-butyl ester**
 4-Fluoro-2-methyl-1-nitrobenzene (2 g), piperazine-1-carboxylic acid *tert*-butyl ester
 (4.8 g), potassium carbonate (3.57 g) and dimethyl sulfoxide (20 ml) were heated together
 at 80 °C under nitrogen for 15 hours. The mixture was then cooled, diluted with ethyl
 acetate (200 ml), washed with 2M aqueous hydrochloric acid (200 ml), dried (MgSO₄), and
 10 concentrated to give the sub-title compound (4.05 g).

MS (APCI+ve) 321 (M)⁺

¹H NMR (DMSO-d₆) δ 8.02 - 7.98 (1H, d), 6.89 - 6.86 (2H, m), 3.45 (8H, s), 2.55 (3H, s),
 1.42 (9H, s).

15

b) **4-(4-Amino-3-methylphenyl)-piperazine-1-carboxylic acid *tert*-butyl ester**
 4-(3-Methyl-4-nitrophenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (2 g), iron
 powder (1.74 g), ammonium chloride (1.67 g), ethanol (50 ml) and water (50 ml) were
 refluxed together under nitrogen for 2 hours. The mixture was cooled and the iron was
 20 filtered off. Water (200 ml) was added to the residue and the product extracted into ethyl
 acetate (3 x 200 ml), dried (MgSO₄), and concentrated to give the sub-title compound
 (1.20 g).

¹H NMR (DMSO-d₆) δ 6.62 - 6.52 (3H, m), 4.38 (2H, s), 3.41 (4H, br s), 2.83 (4H, br s),
 25 2.02 (3H, s), 1.41 (9H, s).

c) 2-(3,4-Difluoro-phenylamino)-N-(2-methyl-5-piperazin-1-yl-phenyl)-acetamide, trihydrochloride

Prepared according to the procedures for Examples 4d), 4e) & 4f), without characterisation of intermediates, 4-(3-amino-4-methyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (490mg) gave the title compound (200mg) as the trihydrochloride.

Melting Point: >230°C

MS (APCI+ve) 361 (M+H)⁺ for free base

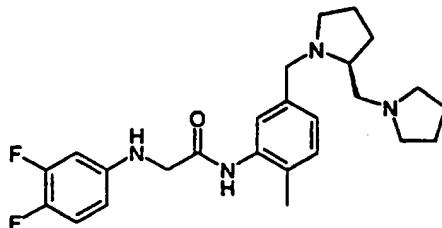
¹H NMR (DMSO-d₆) δ 9.32 (1H, s), 9.22 (2H, brs), 7.22 (1H, d), 7.14 (1H, q), 6.85

(1H, d), 6.80 (1H, dd), 6.62 (1H, ddd), 6.41 (1H, brd), 6.03 (2H, brs), 3.91 (2H, brs), 3.35 (4H, brs), 3.20 (4H, brs), 2.08 (3H, s).

Example 11

(S)-2-(3,4-Difluoro-phenylamino)-N-(2-methyl-5-(2-pyrrolidin-1-ylmethyl-pyrrolidin-

15 1-ylmethyl)-phenyl)-acetamide



a) 5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methyl-phenylamine

Prepared according to the procedure of Example 3a) using (3-amino-4-methyl-phenyl)-methanol (1.61 g), afforded the sub-title compound as a pale brown oil (2.13 g).

20

¹H NMR (DMSO-d₆) δ 6.85 (1H, d), 6.55 (1H, s), 6.39 (1H, d), 4.77 (2H, s), 4.52 (2H, s), 2.01 (3H, s), 0.89 (9H, s), 0.06 (6H, s).

b) (3,4-Difluoro-phenyl)-[(5-hydroxymethyl-2-methyl-phenylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester

Prepared according to the method of Example 3b), from 5-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-methyl-phenylamine (2.0 g) and [*tert*-butoxycarbonyl-(3,4-difluorophenyl)-amino]-acetic acid (2.30 g) to give the sub-title product (1.9 g) as a white solid.

¹H NMR (DMSO-d₆) δ 9.42 (1H, s), 7.49-7.32 (3H, m), 7.24 (1H, m), 7.15 (1H, d), 7.03 (1H, d), 5.13 (1H, t), 4.43 (1H, d), 4.38 (1H, s), 2.15 (3H, s), 1.39 (9H, s).

10

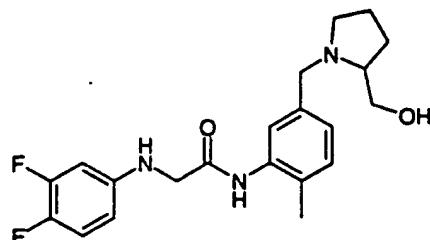
c) (S)-2-(3,4-Difluoro-phenylamino)-N-(2-methyl-5-(2-pyrrolidin-1-ylmethyl)-pyrrolidin-1-ylmethyl)-phenyl)-acetamide

To a solution of (3,4-difluoro-phenyl)-[(5-hydroxymethyl-2-methyl-phenylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester (0.203 g) in dry 1-methyl-2-pyrrolidinone (2 ml) was added *N,N*-diisopropylethylamine (0.52 ml) followed by methanesulfonyl chloride (0.14 ml) in a single portion. After 3 hours, the reaction was poured into diethylether / water. The organic layer was separated and washed sequentially with water, aqueous KHSO₄ and aqueous NaHCO₃. The organics were then dried (Na₂SO₄) and concentrated. The resulting residue was dissolved in 1-methyl-2-pyrrolidinone (5 ml) and *N,N*-diisopropylethylamine (0.17 ml) added. An aliquot (50mL) was removed and added to (S)-(+)-1-(2-pyrrolidinylmethyl)-pyrrolidine (125 mL of a 0.2 M solution in 0.4 M *N,N*-diisopropylethylamine in 1-methyl-2-pyrrolidinone) and the reaction heated at 95 °C for 24 hours. After cooling to room temperature, the volatiles were removed *in vacuo*. Methanol (100 mL) was added, and after dissolution of the mixture, HCl (150 mL of a 4 M solution in dioxane) was added and the reaction stirred for a further 16 hours. The volatiles were removed and dimethyl sulfoxide (500 mL) was added to give the title compound as a 10 mM solution. An aliquot (30 mL) of this solution was diluted with dimethyl sulfoxide / water (220 mL of a 1:1 mixture) was analysed by HPLC on a 20mm x 3.9mm Waters Symmetry C8 column, eluting with 30% - 95% acetonitrile / ammonium acetate.

MS (APCI +ve) 443 (M+H)⁺

Example 12

5 (S)-2-(3,4-Difluoro-phenylamino)-N-[5-(2-hydroxymethyl-pyrrolidin-1-ylmethyl)-2-methyl-phenyl]-acetamide

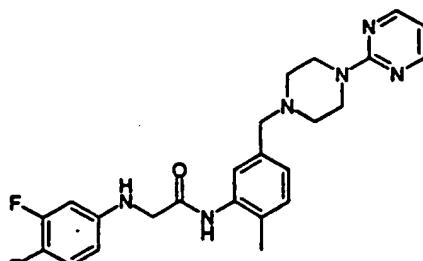


Prepared according to the procedure of Example 11c) using (3,4-difluoro-phenyl)-[(5-hydroxymethyl-2-methyl-phenylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester and 10 (S)-(+)-2-pyrrolidinemethanol to give the title compound as a 10 mM solution in dimethyl sulfoxide. An aliquot (30 mL) of this solution was diluted with dimethyl sulfoxide / water (220 mL of a 1:1 mixture) was analysed by HPLC on a 20mm x 3.9mm Waters Symmetry C8 column, eluting with 30% - 95% acetonitrile / ammonium acetate.

15 MS (APCI +ve) 390 (M+H)⁺

Example 13

20 2-(3,4-Difluoro-phenylamino)-N-[2-methyl-5-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-phenyl]-acetamide



20

Prepared according to the procedure of Example 11c) using (3,4-difluoro-phenyl)-[(5-hydroxymethyl-2-methyl-phenylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester and

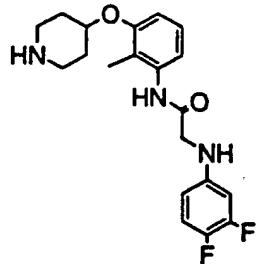
1-(2-pyrimidyl)piperazine dihydrochloride to give the title compound as a 10 mM solution in dimethyl sulfoxide. An aliquot (30 mL) of this solution was diluted with dimethyl sulfoxide / water (220 mL of a 1:1 mixture) was analysed by HPLC on a 20mm x 3.9mm Waters Symmetry C8 column, eluting with 30% - 95% acetonitrile / ammonium acetate.

5

MS (APCI +ve) 453 (M+H)⁺

Example 14

2-(3,4-Difluorophenylamino)-N-[2-methyl-3-(piperidin-4-yloxy)phenyl]acetamide trifluoroacetate



a) 3-(*tert*-Butyl-dimethyl-silyloxy)-2-methyl-phenylamine

The subtitle compound was prepared from 3-amino-o-cresol (1.83g) by the method of Example 8 step (a).

15

MS (APCI) 238 (M+H)

¹H NMR (CDCl₃) δ 6.86 (1H,t), 6.33 (1H,d), 6.28 (1H,d), 3.59 (2H, brs), 2.04 (3H,s), 1.01 (9H,s), 0.20 (6H,s).

20

b) N-[3-(*tert*-Butyl-dimethyl-silyloxy)-2-methyl-phenyl]-2-chloroacetamide

The subtitle compound was prepared from the product of step (a) (3.25g) by the method of example 4 step (d). Yield 4.2g.

25

MS (APCI) 405 (M-H)

¹H NMR (CDCl₃) δ 8.22 (1H, brs), 7.49 (1H,d), 7.09 (1H,t), 6.69 (1H,d), 4.23 (2H,s), 2.16 (3H,s), 1.02 (9H,s), 0.22 (6H,s).

c) ***N*-(3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-phenyl]-2-(3,4-difluoro-phenylamino)-acetamide**

The subtitle compound was prepared from the product of step (b) (4.2g) by the 5 method of Example 4 step (e). Yield 1.71g.

MS (APCI) 405 (M-H)

¹H NMR (CDCl₃) δ 8.38 (1H,s), 7.55 (1H,d), 7.10-6.99 (2H,m), 6.63 (1H,d), 6.54 (1H,m), 6.40 (1H, br d), 4.39 (1H,br t), 3.91 (2H,d), 1.94 (3H,s), 0.99 (9H,s), 0.19 (6H,s).

10

d) **2-(3,4-Difluorophenylamino)-*N*-(3-hydroxy-2-methylphenyl)acetamide**

A solution of tetrabutylammonium fluoride in THF (1M, 4.6ml) was added to a solution of the product from step (c) (1.71g) in THF (20ml). The mixture was stirred at room temperature for 1 hour and evaporated to dryness. The residue was purified by flash 15 chromatography eluting with 3% ethanol (EtOH) in dichloromethane (CH₂Cl₂) to give the product as a white solid. Yield 0.82g.

Melting point: 216°C (dec)

MS (APCI) 291 (M-H)

20 ¹H NMR (DMSO-d₆) δ 9.34 (1H,s), 9.27 (1H,s), 7.15 (1H,q), 6.94 (1H,m), 6.87 (1H,d), 6.64 (1H,d), 6.58 (1H,m), 6.39 (1H,br d), 6.30 (1H,t), 3.85 (2H,d), 1.92 (3H,s).

e) **2-(3,4-Difluorophenylamino)-*N*-[2-methyl-3-(piperidin-4-yloxy)phenyl]acetamide trifluoroacetate**

25 Tributylphosphine (0.55ml) was added to a mixture of 4-hydroxypiperidine-1-carboxylic acid *tert*-butyl ester (0.44g), and the product from step (d) (0.25g) and 1,1'-(azodicarbonyl)dipiperidine (0.55g) in tetrahydrofuran (10ml). The mixture was heated at 60°C under nitrogen (N₂) for 2.5 hours. A further 0.55ml tributylphosphine, 0.44g 4-hydroxypiperidine-1-carboxylic acid *tert*-butyl ester and 0.55g 30 1,1'-(azodicarbonyl)dipiperidine were added and heating was continued for 3 hours. The

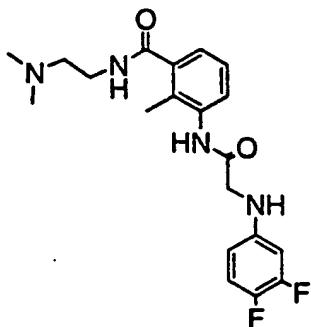
mixture was cooled to room temperature, diluted with ether and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography eluting with 1% EtOH in CH_2Cl_2 . The product was dissolved in CH_2Cl_2 (10ml) and treated with trifluoroacetic acid (10ml). After 2 hours the reaction mixture was concentrated *in vacuo* and the residue was triturated with diethyl ether to give the trifluoroacetic acid salt of the product as a white solid. Yield 130mg.

MS (APCI) 376 (M+H)

^1H NMR (DMSO-d₆) δ 9.40 (1H,s), 8.55 (1H,br s), 8.44 (1H, br s), 7.20-7.09 (2H,m), 7.03 (1H,d), 6.88 (1H,d), 6.63-6.55 (1H,m), 6.40 (1H,d), 4.63 (1H,m), 3.87 (2H,s), 3.21 (2H,d), 3.11 (2H, br s), 2.05 (2H,m), 1.98 (3H,s), 1.83 (2H,m).

Example 15

15 3-[2-(3,4-Difluorophenylamino)acetylamino]-N-(2-dimethylaminoethyl)-2-methylbenzamide



a) 3-Amino-2-methylbenzoic acid, methyl ester

Trimethylsilyl chloride (5ml) was added to a solution of 3-amino-2-methylbenzoic acid (3g) in methanol (100ml). The mixture was heated at reflux for 2 hours and 20 concentrated *in vacuo* to give the hydrochloride salt. Yield 4.0g.

^1H NMR (DMSO-d₆) δ 7.60 (1H,d), 7.54 (1H,d), 7.35 (1H,t), 3.84 (3H,s), 2.42 (2H,s).

b) 3-(2-Chloro-acetylamino)-2-methylbenzoic acid, methyl ester

The subtitle compound was prepared from the product of step (a) (4.0g) by the method of Example 4 step (d). Yield 4.8g.

5 MS (APCI) 240 (M-1)

¹H NMR (CDCl₃) δ 8.31 (1H,br s), 7.99 (1H,d), 7.71 (1H,d), 7.30 (1H,t), 4.26 (2H,s), 3.91 (3H,s), 2.51 (3H,s).

10 **c) 3-[2-(3,4-Difluorophenylamino)-acetylamino]-2-methylbenzoic acid, methyl ester**

The title compound was prepared from the product of step (b) (6.68g) by the method of Example 4 step (e). Yield 1.42g.

15 ¹H NMR (DMSO-d₆) δ 9.59 (1H,s), 7.56 (1H,d), 7.53 (1H,d), 7.16 (1H,q), 6.60 (1H,m), 6.40 (1H,br d), 6.32 (1H,t), 3.90 (2H,d), 3.82 (3H,s), 2.26 (3H,s).**d) 3-[2-(3,4-Difluorophenylamino)-acetylamino]-2-methylbenzoic acid**

A mixture of the product from step (c) (1.33g) and lithium hydroxide monohydrate (0.84g) in methanol (120ml) and water (25ml) was heated at reflux for 2 hours, cooled and 20 concentrated *in vacuo*. The residual aqueous solution was acidified with glacial acetic acid and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried (MgSO₄) and evaporated to give a cream solid. Yield 1.27g.

Melting point: 198°C (dec)

25 MS (APCI) 319 (M-H)

¹H NMR (DMSO-d₆) δ 12.92 (1H,br s), 9.55 (1H,s), 7.57 (1H,d), 7.49 (1H,d), 7.28 (1H,m), 7.16 (1H,q), 6.60 (1H,m), 6.40 (1H,br d), 6.32 (1H,t), 3.90 (2H,d), 2.28 (3H,s).

e) 3-[2-(3,4-Difluorophenylamino)acetylaminol]-N-(2-dimethylaminoethyl)-2-methylbenzamide

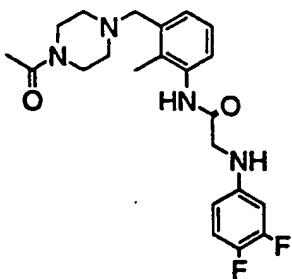
A mixture of 3-[2-(3,4-difluorophenylamino)acetylaminol]-2-methylbenzoic acid (0.2g), *N,N*-dimethylethylenediamine (0.08ml), bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP[®]) (0.34g), dimethylaminopyridine (0.07g) and *N,N*-diisopropylethylamine (0.31ml) in dimethylformamide (5ml) was stirred at room temperature under N₂ for 18 hours. The reaction mixture was partitioned between ethyl acetate and water and the organic phase was washed with water and brine, dried (MgSO₄) and evaporated. The crude product was triturated with diethyl ether. The resultant solid was triturated with ethyl acetate and filtered. Yield 70mg.

MS (APCI) 391 (M+H)

¹H NMR (DMSO-d₆) δ 9.44 (1H,s), 8.15 (1H,t), 7.42 (1H,d), 7.22-7.07 (3H,m), 6.63-6.56 (1H,m), 6.40 (1H,d), 6.31 (1H,t), 3.89 (2H,d), 3.28 (2H,m), 2.37 (2H,t), 2.17 (6H,s), 2.10 (3H,s).

Example 16

N-[3-(4-Acetyl-piperazin-1-ylmethyl)-2-methylphenyl]-2-(3,4-difluorophenylamino)acetamide



20

a) 3-(*tert*-Butyl-dimethylsilyloxyethyl)-2-methylphenylamine

The subtitle compound was prepared from 3-amino-2-methylbenzyl alcohol (2.0g) by the method of Example 8 step (a).

¹H NMR (CDCl₃) δ 7.01 (1H,t), 6.85 (1H,d), 6.64 (1H,d), 4.69 (2H,s), 3.59 (2H,brs), 2.08 (3H,s), 0.93 (9H,s), 0.10 (6H,s).

b) *N*-[3-(*tert*-Butyl-dimethyl-silyloxyethyl)-2-methylphenyl]-2-chloroacetamide

5 The subtitle compound was prepared from the product of step (a) (1.0g) by the method of Example 4 step (d). Yield 1.3g.

MS (APCI) 292 (M-Cl)

¹H NMR (CDCl₃) δ 8.22 (1H,brs), 7.66 (1H,d), 7.32-7.21 (2H, m), 4.71 (2H,s), 2.20 (3H, s), 0.94 (9H,s), 0.01 (6H,s).

c) *N*-[3-(*tert*-Butyl-dimethyl-silyloxyethyl)-2-methylphenyl]-2-(3,4-difluoro-phenylamino)acetamide

15 The subtitle compound was prepared from the product of step (b) (1.3g) by the method of Example 4 step (e). Yield 1.03g.

MS (APCI) 419 (M-H)

¹H NMR (CDCl₃) δ 8.37 (1H,s), 7.71 (1H,d), 7.26-7.19 (2H,m), 7.01 (1H,q), 6.56-6.51 (1H,m), 6.40 (1H,m), 4.66 (2H,s), 3.92 (2H,d), 1.99 (3H,s), 0.91 (9H,s), 0.07 (6H,s).

20 d) 2-(3,4-Difluorophenylamino)-*N*-(3-hydroxymethyl-2-methylphenyl)acetamide

The sub-title compound was prepared from the product of step (c) by the method of Example 14 step (d).

25 Melting point: 155°C (dec)

MS (APCI) 307 (M+H)

¹H NMR (DMSO-d₆) δ 9.40 (1H,s), 7.24-7.12 (4H,m), 6.63-6.56 (1H,m), 6.42-6.39 (1H,m), 6.31 (1H,t), 5.08 (1H,t), 4.48 (2H,d), 3.07 (2H,d), 2.02 (3H,s).

e) *N*-[3-(4-Acetyl-piperazin-1-ylmethyl)-2-methylphenyl]-2-(3,4-difluorophenylamino)acetamide

Methane sulphonyl chloride (0.06ml) was added to a solution of the product of step (d) (0.12g) and *N,N*-diisopropylethylamine (0.28ml) in tetrahydrofuran (3ml). The reaction mixture was stirred at room temperature for 1.5 hours. A solution of 1-acetyl piperazine (0.15g) in tetrahydrofuran (1ml) was added and the mixture was heated at reflux for 2 hours. The reaction mixture was partitioned between ethyl acetate and water and the organic phase was washed with water and brine, dried ($MgSO_4$) and evaporated. The crude product was triturated with ethyl acetate/iso hexane to give the product as a pale yellow solid.

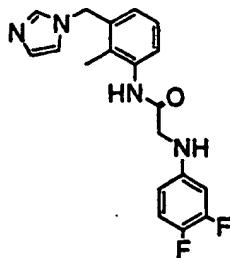
Yield 0.1g.

MS (APCI) 417 (M+H)

1H NMR (DMSO- d_6) δ 9.39 (1H,s), 7.28 (1H,d), 7.20-7.06 (3H,m), 6.60 (1H,m), 6.40 (1H,br d), 6.32 (1H,t), 3.88 (2H,d), 3.43 (2H,s), 3.37 (4H,m), 2.34 (2H,m), 2.29 (2H,m), 2.12 (3H,s), 1.97 (3H,s).

Example 17

2-(3,4-Difluorophenylamino)-*N*-(3-imidazol-1-ylmethyl-2-methylphenyl)acetamide



20

The title compound was prepared from imidazole by the method of Example 16.

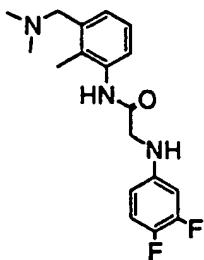
Melting point: 160°C (dec)

MS (APCI) 357 (M+H)

¹H NMR (DMSO-d₆) δ 9.47 (1H,s), 7.66 (1H,s), 7.30 (1H,d), 7.19-7.12 (2H,m), 7.07 (1H,s), 6.91 (1H,s), 6.78 (1H,d), 6.62-6.56 (1H,m), 6.35 (1H,d), 6.29 (1H,t), 5.23 (2H,s), 3.87 (2H,d), 2.05 (3H,s).

5 **Example 18**

2-(3,4-Difluorophenylamino)-N-(3-dimethylaminomethyl-2-methylphenyl)acetamide



10 The title compound was prepared by the method of Example 16 using dimethylamine solution in tetrahydrofuran (2M).

Melting point: 144°C (dec)

MS (APCI) 334 (M+H)

15 ¹H NMR (DMSO-d₆) δ 10.07 (1H,br s), 9.60 (1H,s), 7.45 (1H,d), 7.39 (1H,d), 7.27 (1H,m), 7.16 (1H,q), 6.64-6.59 (1H,m) 6.42 (1H,d), 4.33 (2H,d), 3.91 (2H,s), 2.73 (3H,s), 2.72 (3H,s), 2.18 (3H,s).

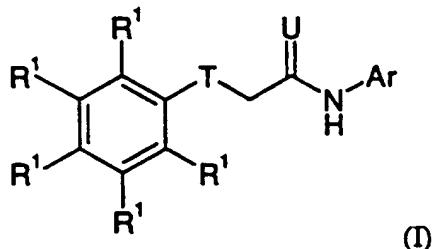
Pharmacological Analysis

20 Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the P2X₇ receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3), p.126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. The increase in fluorescence can be used as a measure of P2X₇ receptor activation and therefore to quantify the effect of a compound on the P2X₇ receptor.

In this manner, each of the title compounds of Examples 1 to 18 was tested for antagonist activity at the P2X₇ receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 250 µl of test solution comprising 200 µl of a suspension of THP-1 cells (2.5×10^6 cells/ml) containing 10^{-4} M ethidium bromide, 25 µl of a high potassium buffer solution containing 10^{-5} M bbATP, and 25 µl of the high potassium buffer solution containing 3×10^{-5} M test compound. The plate was covered with a plastics sheet and incubated at 37 °C for one hour. The plate was then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a P2X₇ receptor agonist) and pyridoxal 5-phosphate (a P2X₇ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC₅₀ figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of Examples 1 to 18 demonstrated antagonist activity, having a pIC₅₀ figure > 4.50.

CLAIMS

1. A compound of general formula

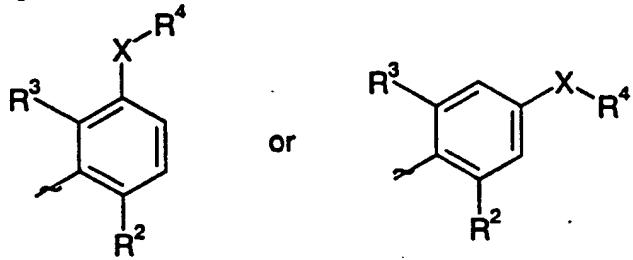


5 wherein:

each R^1 independently represents a hydrogen or halogen atom, or a trifluoromethyl, cyano, nitro, C_1 - C_6 alkyl or C_1 - C_6 alkoxy group;

T represents an oxygen atom or a group NH ;

U represents an oxygen or sulphur atom or a group NH ;

10 Ar represents a group

X represents a bond, an oxygen atom or a group CO , CH_2 , CH_2O , $O(CH_2)_m$,

CH_2OCH_2 , NR^5 , CH_2NR^5 , NR^5CH_2 , $CH_2NR^5CH_2$, $CONR^5$, $S(O)_n$ or SO_2NR^5 ;

m is 1, 2 or 3;

15 n is 0, 1 or 2;

one of R^2 and R^3 represents a halogen, cyano, nitro, amino, hydroxyl, or a group selected from C_1 - C_6 alkyl optionally substituted by at least one C_3 - C_6 cycloalkyl,

C_3 - C_8 cycloalkyl, C_1 - C_6 alkyloxy optionally substituted by at least one C_3 - C_6 cycloalkyl,

C_3 - C_8 cycloalkyloxy, $S(O)_pC_1$ - C_6 alkyl or $S(O)_qC_3$ - C_8 cycloalkyl, each of these groups

20 being optionally substituted by one or more fluorine atoms, and the other of R^2 and R^3 represents a hydrogen or halogen atom or a methyl group;

p is 0, 1 or 2;

q is 0, 1 or 2;

R⁴ represents di(C₁₋₂ alkyl)N(CH₂)_t where t is 0, 1 or 2 or imidazolyl, or R⁴ represents a 3- to 9-membered saturated heterocyclic ring system containing one or two nitrogen atoms, the heterocyclic ring system being optionally substituted by one or more

5 substituents independently selected from fluorine atoms, hydroxyl, C₁-C₆ alkyl, acetyl, hydroxyC₁-C₆ alkyl, -NR⁶R⁷, -(CH₂)₁NR⁶R⁷, -CONR⁶R⁷ and pyrimidinyl, or R⁴ represents a 3- to 8-membered saturated carbocyclic ring system substituted by one or more substituents independently selected from NR⁶R⁷, -(CH₂)₁NR⁶R⁷ and -CONR⁶R⁷, the ring system being optionally further substituted by one or more substituents

10 independently selected from fluorine atoms, hydroxyl and C₁-C₆ alkyl;

r is 1, 2, 3, 4, 5 or 6;

R⁵ represents a hydrogen atom or a C₁-C₆ alkyl or C₃-C₈ cycloalkyl group; and

R⁶ and R⁷ each independently represent a hydrogen atom or a C₁-C₆ alkyl or C₃-C₈ cycloalkyl group, or R⁶ and R⁷ together with the nitrogen atom to which they are

15 attached form a 3- to 8-membered saturated heterocyclic ring, provided that when R³ represents a cyano group, then X is other than a bond; or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein T represents a group NH.

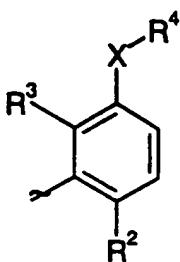
20

3. A compound according to claim 1 or claim 2, wherein U represents an oxygen atom.

4. A compound according to any one of claims 1 to 3, wherein each R¹ independently represents a hydrogen or halogen atom.

25

5. A compound according to any one of the preceding claims, wherein Ar represents a group



6. A compound according to any one of the preceding claims, wherein one of R^2 and R^3 represents a halogen, cyano, nitro, amino, hydroxyl, or a group selected from C_1 - C_4 alkyl optionally substituted by at least one C_5 - C_6 cycloalkyl, C_5 - C_6 cycloalkyl, C_1 - C_4 alkyloxy optionally substituted by at least one C_5 - C_6 cycloalkyl, C_5 - C_6 cycloalkyloxy, $S(O)_pC_1$ - C_4 alkyl or $S(O)_qC_5$ - C_6 cycloalkyl, each of these groups being optionally substituted by one to four fluorine atoms, and the other of R^2 and R^3 represents a hydrogen or halogen atom.

10

7. A compound according to any one of the preceding claims, wherein R^4 represents a 3- to 9-membered saturated heterocyclic ring system containing one or two nitrogen atoms, the heterocyclic ring system being optionally substituted by one to four substituents independently selected from fluorine atoms, hydroxyl, C_1 - C_6 alkyl, hydroxy C_1 - C_6 alkyl, $-NR^6R^7$, $-(CH_2)_rNR^6R^7$, $-CONR^6R^7$ and pyrimidinyl.

15

8. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, according to claim 1 being:

2-(3,4-Difluorophenylamino)-*N*-(2-methyl-5-piperazin-1-ylmethyl-phenyl)-acetamide, trihydrochloride,

2-(3,4-Difluoro-phenylamino)-*N*-(2-methyl-5-piperazin-1-ylmethyl-phenyl)-thioacetamide,

2-(3,4-Difluoro-phenylamino)-*N*-(2-methyl-4-piperazin-1-ylmethyl-phenyl)-acetamide, trihydrochloride,

N-(2-Chloro-5-piperazin-1-yl-phenyl)-2-(3,4-difluoro-phenylamino)-acetamide, trihydrochloride,

(*S*)-2-(3,4-Difluoro-phenylamino)-*N*-[2-methyl-4-(2-pyrrolidin-1-ylmethyl-pyrrolidin-1-ylmethyl)-phenyl]-acetamide, trihydrochloride,

2-(3-Chloro-4-fluorophenylamino)-*N*-(2-methyl-5-[3-(4-methylpiperazin-1-yl)-propoxyl]phenyl)acetamide,

5 (+/-)-2-(3-Chloro-4-fluoro-phenylamino)-*N*-[2-methyl-5-(piperidin-4-yloxy)-phenyl]-acetamide, dihydrochloride,

2-(3,4-Difluoro-phenylamino)-*N*-[2-methyl-4-(piperidin-4-yloxy)-phenyl]-acetamide, dihydrochloride,

10 (\pm)-*N*-[5-(3-Amino-pyrrolidin-1-yl)-2-methyl-phenyl]-2-(3,4-difluoro-phenylamino)-acetamide, trihydrochloride,

2-(3,4-Difluoro-phenylamino)-*N*-(2-methyl-5-piperazin-1-yl-phenyl)-acetamide, trihydrochloride,

15 (*S*)-2-(3,4-Difluoro-phenylamino)-*N*-(2-methyl-5-(2-pyrrolidin-1-ylmethyl-pyrrolidin-1-ylmethyl)-phenyl)-acetamide,

20 (+/-)-2-(3,4-Difluoro-phenylamino)-*N*-[5-(2-hydroxymethyl-pyrrolidin-1-ylmethyl)-2-methyl-phenyl]-acetamide,

2-(3,4-Difluoro-phenylamino)-*N*-[2-methyl-5-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-phenyl]-acetamide,

25 2-(3,4-Difluorophenylamino)-*N*-[2-methyl-3-(piperidin-4-yloxy)phenyl]acetamide trifluoroacetate,

3-[2-(3,4-Difluorophenylamino)acetylamino]-*N*-(2-dimethylaminoethyl)-2-methylbenzamide,

30 *N*-[3-(4-Acetyl-piperazin-1-ylmethyl)-2-methylphenyl]-2-(3,4-difluorophenylamino)acetamide,

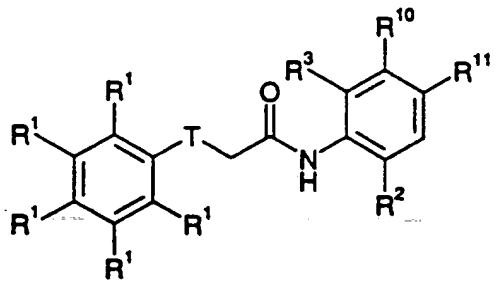
2-(3,4-Difluorophenylamino)-*N*-(3-imidazol-1-ylmethyl-2-methylphenyl)acetamide,

or

2-(3,4-Difluorophenylamino)-*N*-(3-dimethylaminomethyl-2-methylphenyl)acetamide.

9. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises:

(i) when U represents an oxygen atom, X represents a CH_2 group and R^4 represents a 3- to 8-membered saturated heterocyclic ring system containing one or two nitrogen atoms, the heterocyclic ring system being optionally substituted by one or more substituents independently selected from fluorine atoms, hydroxyl, $\text{C}_1\text{-C}_6$ alkyl, hydroxy $\text{C}_1\text{-C}_6$ alkyl, $-\text{NR}^6\text{R}^7$, $-(\text{CH}_2)_r\text{NR}^6\text{R}^7$, $-\text{CONR}^6\text{R}^7$ and pyrimidinyl, reacting a compound of general formula



(II)

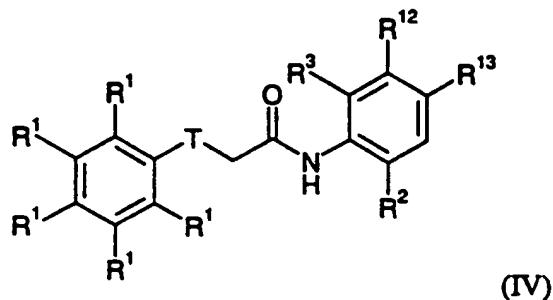
wherein one of R^{10} and R^{11} represents a hydrogen atom and the other of R^{10} and R^{11} represents a group $-\text{CH}_2\text{L}^1$ in which L^1 represents a leaving group, and T , R^1 , R^2 and R^3 are as defined in formula (I), with a compound of general formula



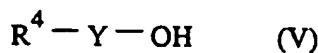
15 in the presence of a base, wherein $\text{R}^{4'}$ represents a 3- to 8-membered saturated heterocyclic ring system containing one or two nitrogen atoms, the heterocyclic ring system being optionally substituted by one or more substituents independently selected from fluorine atoms, hydroxyl, $\text{C}_1\text{-C}_6$ alkyl, hydroxy $\text{C}_1\text{-C}_6$ alkyl, $-\text{NR}^6\text{R}^7$, $-(\text{CH}_2)_r\text{NR}^6\text{R}^7$, $-\text{CONR}^6\text{R}^7$ and pyrimidinyl and wherein R^6 and R^7 are as defined in formula (I); or

20

(ii) when U represents an oxygen atom and X represents an oxygen atom or a group $\text{O}(\text{CH}_2)_m$, reacting a compound of general formula

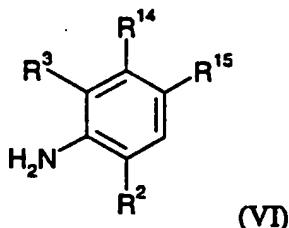


wherein one of R^{12} and R^{13} represents a hydrogen atom and the other of R^{12} and R^{13} represents a hydroxyl group, and T , R^1 , R^2 and R^3 are as defined in formula (I), with a compound of general formula

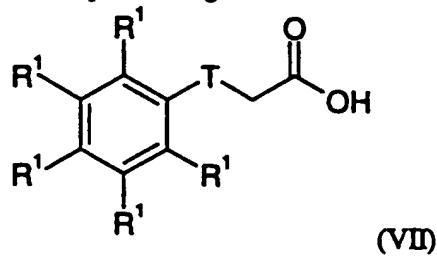


wherein Y represents a bond or a group $(CH_2)_m$ and m and R^4 are as defined in formula (I), in the presence of 1,1-(azodicarbonyl)dipiperidine and tributylphosphine; or

10 (iii) when U represents an oxygen atom and X represents a bond, an oxygen atom or a group $O(CH_2)_m$, NR^5 , NR^5CH_2 , CO , $CONR^5$, SO_2 or SO_2NR^5 reacting a compound of general formula

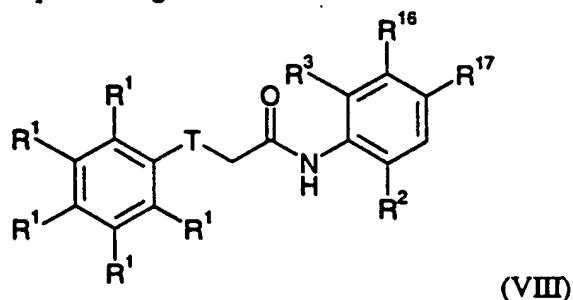


15 wherein one of R^{14} and R^{15} represents a group $-X'-R^4$ and the other of R^{14} and R^{15} represents a hydrogen atom, X' represents a bond, an oxygen atom or a group $O(CH_2)_m$, NR^5 , NR^5CH_2 , CO , $CONR^5$, SO_2 or SO_2NR^5 , and m , R^2 , R^3 , R^4 and R^5 are as defined in formula (I), with a compound of general formula



wherein T and R¹ are as defined in formula (I), in the presence of a coupling reagent and a base; or

5 (iv) when U represents an oxygen atom and X represents a bond or a group NR⁵ or NR⁵CH₂, reacting a compound of general formula



wherein one of R¹⁶ and R¹⁷ represents a leaving group, L², and the other of R¹⁶ and R¹⁷ represents a hydrogen atom and T, R¹, R² and R³ are as defined in formula (I), with a compound of general formula



wherein Z represents a hydrogen atom or a group NHR⁵ or CH₂NHR⁵ and R⁴ and R⁵ are as defined in formula (I), optionally in the presence of a palladium catalyst, a phosphine ligand and a base; or

15 (v) when U represents an oxygen atom and X represents a group CH₂O, reacting a compound of formula (II) as defined in (i) above with a compound of formula (V) as defined in (ii) above wherein Y represents a bond, in the presence of a base or in the presence of a metal salt; or

20 (vi) when U represents an oxygen atom and X represents a group CH₂NR⁵, reacting a compound of formula (II) as defined in (i) above with a compound of formula (IX) as defined in (iv) above wherein Z represents a group NHR⁵; or

(vii) when U represents an oxygen atom and X represents a group CH₂OCH₂,
25 reacting a compound of formula (II) as defined in (i) above with a compound of formula

(V) as defined in (ii) above wherein Y represents a group CH_2 , in the presence of a base or in the presence of a metal salt; or

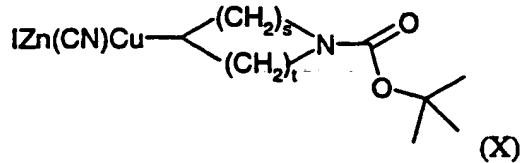
(viii) when U represents an oxygen atom and X represents a group $\text{CH}_2\text{NR}^5\text{CH}_2$,

5 reacting a compound of formula (II) as defined in (i) above with a compound of formula (IX) as defined in (iv) above wherein Z represents a group CH_2NHR^5 ; or

(ix) when U represents an oxygen atom, X represents a group CH_2 and R^4

represents an unsubstituted 4- to 6-membered saturated heterocyclic ring system containing

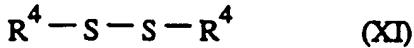
10 one nitrogen atom, reacting a compound of formula (II) as defined in (i) above, with a compound of general formula



wherein s and t independently represent 1 or 2; or

15

(x) when U represents an oxygen atom and X represents a sulfur atom, reacting a compound of formula (VIII) as defined in (iv) above, with n-butyllithium and then with a compound of general formula



20 wherein R^4 is as defined in formula (I); or

(xi) when U represents an oxygen atom and X represents a CH_2 group, reacting a compound of formula (VIII) as defined in (iv) above, with n-butyllithium and then with a compound of general formula



25 wherein R^4 is as defined in formula (I), followed by a reduction reaction; or

(xii) when U represents an oxygen atom and X represents a bond, reacting a compound of formula (VIII) as defined in (iv) above, with n-butyllithium and then with a compound of general formula

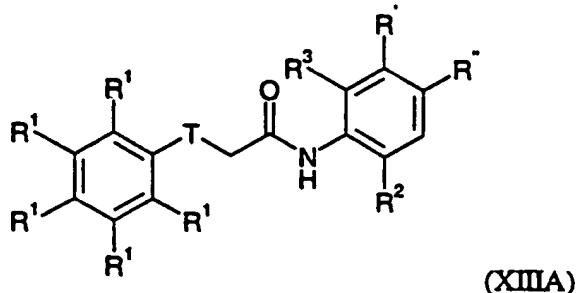


wherein R^4 is as defined in formula (I), followed by a reduction reaction; or

(xiii) when U represents a sulphur atom, reacting a corresponding compound of formula (I) in which U represents an oxygen atom with a thiolating agent; or

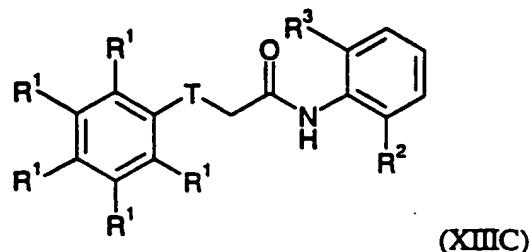
(xiv) when U represents a group NH, reacting a corresponding compound of formula (I) in which U represents a sulphur atom with a suitable alkylating agent followed by reaction with ammonium chloride or ammonia;

(xv) when U represents an oxygen atom and X represents $CONR^5$, reacting a compound of general formula



wherein one of R^1 and R^2 represents a hydrogen atom and the other of R^1 and R^2 represents a carboxyl group and T, R^1 , R^2 and R^3 are as defined in formula (I), with a compound of general formula (XIIIB), $R^4 - NHR^5$, wherein R^4 and R^5 are as defined in formula (I); or

(xvi) when U represents an oxygen atom, X represents CH_2 and R^4 is bonded to X through a nitrogen atom, reacting a compound of general formula



wherein T, R¹, R² and R³ are as defined in formula (I), with methane sulphonyl chloride followed by reaction with a compound of general formula (XIIID), R^{4"} - H, wherein R^{4"} is defined as for R⁴ in formula (I) other than:

- 5 • di(C₁-₂ alkyl)N(CH₂)_t where t is 1 or 2, and
- 3- to 8-membered saturated carbocyclic ring system substituted by one or more substituents independently selected from NR⁶R⁷, -(CH₂)_rNR⁶R⁷ and -CONR⁶R⁷, the ring system being optionally further substituted by one or more substituents independently selected from fluorine atoms, hydroxyl and C₁-C₆ alkyl;

10

and optionally after (i), (ii), (iii), (iv), (v), (vi), (vii), (viii), (ix), (x), (xi), (xii), (xiii), (xiv), (xv) or (xvi) converting the compound of formula (I) to a further compound of formula (I) and/or forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

15

10. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

20

11. A process for the preparation of a pharmaceutical composition as claimed in claim 10 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined in any one of claims 1 to 8 with a pharmaceutically acceptable adjuvant, diluent or carrier.

25

12. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8 for use in therapy.

13. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8 for use in the treatment of rheumatoid arthritis.
14. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8 for use in the treatment of chronic obstructive pulmonary disease.
15. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in therapy.
16. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.
17. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in the treatment of an obstructive airways disease.
18. Use according to claim 17, wherein the obstructive airways disease is asthma or chronic obstructive pulmonary disease.
19. A method of effecting immunosuppression which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8.
20. A method of treating, or reducing the risk of, an obstructive airways disease in a patient suffering from, or at risk of, said disease, which comprises administering to the

patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 8.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/01943

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D295/12	C07D295/08	C07D295/18	C07D207/09	A61K31/40
	A61K31/445	A61K31/495	A61P37/06	C07D211/46	C07D207/14
	C07D207/08	C07D239/42	C07D233/61	C07C237/34	C07C237/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GUNTER METZ ET AL.: "Cloxacepride and Related Compounds: A New Series of Orally Active Antiallergic Compounds" JOURNAL OF MEDICINAL CHEMISTRY., vol. 26, no. 7, July 1983 (1983-07), pages 1065-1070, XP002145326 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 table III, compound 33; page 1067, column 1, middle - page 1069, column 2, last paragraph	1,3,4,6, 9-12,19
X	US 4 294 851 A (GUNTER METZ ET AL.) 13 October 1981 (1981-10-13) column 9, example 14; claims	1,3,4,6, 9-12

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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- *E* earlier document but published on or after the international filing date
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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

21 August 2000

Date of mailing of the international search report

19/09/2000

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INTERNATIONAL SEARCH REPORT

Internat. Application No

PCT/GB 00/01943

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHEMICAL ABSTRACTS, vol. 129, no. 17, 26 October 1998 (1998-10-26) Columbus, Ohio, US; abstract no. 211964n, BENJAMIN D. HUMPHREYS ET AL.: "Isoquinolines as Antagonists of the P2X7 Nucleotide Receptor: High Selectivity for the Human Versus Rat Receptor Homologs" page 114; column 1; XP002145327 abstract & MOL. PHARMACOL., vol. 54, no. 1, 1998, pages 22-32,</p>	1,13-20
A	<p>DE 26 23 228 A (LUDWIG MERCK KG) 1 December 1977 (1977-12-01) page 9; claims; examples</p>	1,10, 12-20
P,A	<p>WO 99 29686 A (ASTRA PHARMACEUTICALS) 17 June 1999 (1999-06-17) claims</p>	1,10, 12-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/01943

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 4294851	A 13-10-1981	DE 2730174	A	22-02-1979
		AT 360972	B	10-02-1981
		AT 477678	A	15-07-1980
		AT 363480	B	10-08-1981
		AT 665379	A	15-01-1981
		CA 1108139	A	01-09-1981
		DE 2861461	D	18-02-1982
		EP 0000174	A	10-01-1979
		IT 1098345	B	07-09-1985
DE 2623228	A 01-12-1977	AT 348990	B	12-03-1979
		AT 348877	A	15-08-1978
		BE 854683	A	16-11-1977
		CA 1091247	A	09-12-1980
		CH 633259	A	30-11-1982
		FR 2352791	A	23-12-1977
		GB 1555723	A	14-11-1979
		NL 7705630	A, B,	28-11-1977
		US 4146637	A	27-03-1979
WO 9929686	A 17-06-1999	AU 1791599	A	28-06-1999